PREDISPOSITION TO POSTVACCINIAL ENCEPHALITIS

Library of Congress Catalog Card Number 60-7323

PRINTED IN THE NETHERLANDS BY
BOEK- EN HANDELSDRUKKERIJ D. REIDEL, DORDRECHT

CONTENTS

Chapter

INTRODUCTION

Of all the preventive measures in the history of Medicine, vaccination has given rise to the most controversy. In the beginning the association of variolation with the much-feared small-pox led to much dissension concerning the advantages, disadvantages and even the dangers of variolation. Later, once vaccination had been introduced and had proved its value, the battle, at least in medical circles, was restricted to the question of post-vaccinial encephalitis. Outside medical circles, especially in theological groups, the problems concerning vaccination remained very much alive. On the one hand special church services were organized in order to celebrate the arrival of the vaccine, on the other hand there were many dissenting and disapproving theological articles and sermons. The dissenting voices became louder and found larger audiences in 1924/5, when Van Bouwdijk Bastiaanse published his first articles concerning post-vaccinial encephalitis. Everyone was shocked. Controls were weakened. Physicians who had previously considered vaccination a valuable preventive measure became hesitant or even stopped vaccinating completely.

This marked the birth of the post-vaccinial encephalitis problem. A vast number of physicians went to work to clear this 'means of preventing a recurrence of smallpox' of the charges brought against it. In order to find the factors involved in causing this feared complication, there followed a series of investigations and theories which resulted in an unending stream of publications.

While some people rejected variolation from the very beginning on the grounds that smallpox was of an endogenous nature, the approach to the problem of post-vaccinial encephalitis was completely different.

True, vague remarks were made about the possibility of endogenous factors playing a role, but they were generally not followed up.

The object of this investigation is to search for this endogenous predisposition in an attempt to bring the problem of post-vaccinal encephalitis closer to a solution.

CHAPTER 1

HISTORICAL SURVEY

On reviewing old East-Asian literature, it appears that the clinical picture of smallpox has been known for some time. How important this disease was in earlier times we do not know but we note that in India there was even a smallpox goddess. The first reports from other places, especially from Europe, came after a considerable lapse of time. The increasing traffic and the migrations of whole populations were responsible for the spread of the disease during the years 400-600 A.D. Consequently, in the 15th century smallpox had become a common disease in Europe. In many places in Europe there appeared foci from which the pox flared out to other areas. In the 18th century, when the chance of infection was still great, the inoculation with variola virus was developed. This in turn resulted in a spread of infectious material while maintaining it locally in an active form. The universality of the infection is reflected in the popular saying of the time "von Pocken und Liebe bleiben nur wenige frei".

Generally smallpox was contracted in childhood. When we consider that an epidemic had a mortality of approximately 30% and that a twelfth of the people died of smallpox, we can form some idea of what an awful threat this was for the population of that time. The many theories concerned with the genesis of smallpox took into consideration this high frequency. Some thought of the possibility of hereditary 'Pox glands' or the spread of infectious material from mother to child.

A different approach to the problem became possible through the discovery of bacteria. The latter explanation attracted much attention and as a result the idea arose that it was not absolutely inevitable that one should contract smallpox. Before this time, just as in the

Library of Congress Catalog Card Number 60-

PRINTED IN THE NETHERLAN
BOEK- EN HANDELSDRUKKERIJ D REID

this brought about among the English aristocracy was understandably great. It caused the English King to have inoculated six convicts who had been sentenced to death. Following the success of this experiment, five orphans were also inoculated' When this latter treatment also succeeded inoculation spread like a fire through the English aristocracy but, quickly, there arose voices condemning the method. The opponents of variolation were divided into two groups: the physicians, who found it difficult to accept a method which was introduced by old women and other laymen, and the theologians, whose strongest argument was that the method originated in the East. In the beginning it appeared that the opponents of variolation would win until, in England, a serious smallpox epidemic developed and the weapon of variolation was put to use. One would have expected this to have established the practice but such was not the case. Again there was resistance and rightly so

Through the use of improper material and the air of charlatanry about the doctors who practised inoculation, this method once again was discredited

Gatte of Pisa (1760) had more success. He introduced the smallpox material into the skin by means of a puncture and this usually led to the development of a mild, generalized exanthema. However, the danger of infection of others by the inoculated remained and, in addition, the method was costly and time-consuming. This development in the European countries led to the enforcement, in 1840, in many of these countries of a ban on inoculation Fortunately, other facts which offered more hope had become known From many countries (India, Peru, Mexico, England, France and Germany) came reports of people who remained well during smallpox epidemics and who were known to have been infected earlier with cowpox' Hellwag (1801) reported a case of a girl who attempted in 1772 to infect herself by milking animals with cowpox When this did not succeed, on the advice of a milkmaid she wounded herself and rubbed cowpox in the wound A later inoculation of the same girl with real smallpox material caused no ill effects' Later, several others made use of this same method (the Englishman Jesty in 1774, the Dane Jensen and the German Pleet in 1791) Unfortunately, little value was placed on these facts

The Englishman Jenner, born on May 17, 1749, knew nothing of these cases. In his youth he had heard from the wife of a farmer that having had cowpox had made her immune to smallpox. This led him to begin in 1775 a series of experiments which led to the use of human cowpox lymph for vaccination. On May 14, 1796, the lymph was taken from milkmaid Sarah Nelms and administered to 8-year-old James Phipps. A later inoculation of this boy with variola produced no effect. Jenner's service was mainly in his prolonged series of experiments *stemming from a folktale and his discovery of the* vaccination with human lymph. This discovery made it possible to distribute the vaccine. The result of all this work was that in the beginning of the 19th century vaccination laws were passed in several European countries, beginning with the domains Piombino and Lucca, which had been established by Napoleon and were ruled by his brother-in-law. Vaccination also gained acceptance in countries outside Europe and ships carried human lymph from vaccinated children to other parts of the world (The Phillippines, Peru, etc) Special church services were held to welcome those who brought the lymph The church was even the site for the vaccination In the United States the first vaccination was performed on May 8, 1808, using vaccine from England. Benjamine Waterhouse performed the vaccination on his own son after having read Jenner's reports. (The antagonism which he stirred up by this act made it necessary for him to resign from his position as professor at Harvard University in 1810.)

In opposition to this enthusiasm, there arose antivaccination movements, and, in addition, there were many (among them Jenner) who warned against too great optimism Many of those who protested had already practised inoculation Their warnings about 'Vervichung' now seem comical a vaccinated child became four-footed, another mooed like a cow and yet another coughed like a calf or developed hair over its entire body! However, the warnings concerning failures in the vaccination were more authentic; it appeared that the lymph was often used without proper foresight, mistakes and carelessness were common, laymen administered vaccinations. Consequently, the results of vaccination fell far short of expectations. This proved to be the case in England when, during smallpox epidem-

ics, vaccinated people also fell ill, this did great harm to the reputation of vaccination. The fanatics defended themselves by placing the blame on the use of 'bastard vaccine', but found even better support in the fact that the mortality in the case of vaccinated patients was considerably lower than in the unvaccinated. This is to be seen in the following statistics from the Stockwell Smallpox Hospital, London:

Patients	*Scars*	*Fatalities*
703	none	47 5%
516	one poor	25 0%
632	one good	5.3%
677	two good	4.1%
301	three good	2 3%
259	four or more	1.1%

But this evidence was rejected on the grounds that the vaccinated patients were not recognized as smallpox patients

In this battle, neither of the two sides made a systematic study of the problem. Another question was whether the acquired immunity of a vaccination would last a life-time or would disappear after a number of years. Inasmuch as the facts seemed to point towards the latter, Pearson advised revaccination. This was no discredit to vaccination for there were cases of people having had smallpox twice, and why should the immunity of a vaccination not decrease with time?

Two things were clear from all of these facts (1) it was possible to contract smallpox after vaccination, even though it was generally in a milder form (varioloid); (2) acquired immunity was temporary

Since the danger of smallpox was (and still is) very great in armies the first revaccinations were performed on German military personnel. While previously smallpox had been predominantly a disease of children, the use of vaccination made the second and third decennia the most important and, understandably, the military were the most interested in revaccination. A standardized programme of vaccination of civilians was not yet in force in Germany. England also had difficulties in adopting vaccination regulations Polls were held among governments and physicians and it appeared that the transmission of syphilis was thought to be a great disadvantage, it had

The Englishman Jenner, born on May 17, 1749, knew nothing of these cases. In his youth he had heard from the wife of a farmer that having had cowpox had made her immune to smallpox. This led him to begin in 1775 a series of experiments which led to the use of human cowpox lymph for vaccination. On May 14, 1796, the lymph was taken from milkmaid Sarah Nelms and administered to 8-year-old James Phipps. A later inoculation of this boy with variola produced no effect. Jenner's service was mainly in his prolonged series of experiments stemming from a folktale and his discovery of the vaccination with human lymph This discovery made it possible to distribute the vaccine. The result of all this work was that in the beginning of the 19th century vaccination laws were passed in several European countries, beginning with the domains Piombino and Lucca, which had been established by Napoleon and were ruled by his brother-in-law. Vaccination also gained acceptance in countries outside Europe and ships carried human lymph from vaccinated children to other parts of the world (The Phillippines, Peru, etc.) Special church services were held to welcome those who brought the lymph. The church was even the site for the vaccination. In the United States the first vaccination was performed on May 8, 1808, using vaccine from England. Benjamine Waterhouse performed the vaccination on his own son after having read Jenner's reports. (The antagonism which he stirred up by this act made it necessary for him to resign from his position as professor at Harvard University in 1810)

In opposition to this enthusiasm, there arose antivaccination movements, and, in addition, there were many (among them Jenner) who warned against too great optimism. Many of those who protested had already practised inoculation Their warnings about 'Verviehung' now seem comical a vaccinated child became four-footed, another mooed like a cow and yet another coughed like a calf or developed hair over its entire body' However, the warnings concerning failures in the vaccination were more authentic; it appeared that the lymph was often used without proper foresight, mistakes and carelessness were common, laymen administered vaccinations. Consequently, the results of vaccination fell far short of expectations. This proved to be the case in England when, during smallpox epidem-

ics, vaccinated people also fell ill, this did great harm to the reputation of vaccination The fanatics defended themselves by placing the blame on the use of 'bastard vaccine', but found even better support in the fact that the mortality in the case of vaccinated patients was considerably lower than in the unvaccinated. This is to be seen in the following statistics from the Stockwell Smallpox Hospital, London.

Patients	*Scars*	*Fatalities*
703	none	47.5%
516	one poor	25 0%
632	one good	5.3%
677	two good	4.1%
301	three good	2.3%
259	four or more	1.1%

But this evidence was rejected on the grounds that the vaccinated patients were *not recognized as smallpox patients.*

In this battle, neither of the two sides made a systematic study of the problem Another question was whether the acquired immunity of a vaccination would last a life-time or would disappear after a number of years. Inasmuch as the facts seemed to point towards the latter, Pearson advised revaccination This was no discredit to vaccination for there were cases of people having had smallpox twice, and why should the immunity of a vaccination not decrease with time?

Two things were clear from all of these facts. (1) it was possible to contract smallpox after vaccination, even though it was generally in a milder form (varioloid); (2) acquired immunity was temporary

Since the danger of smallpox was (and still is) very great in armies the first revaccinations were performed on German military personnel While previously smallpox had been predominantly a disease of children, the use of vaccination made the second and third decennia the most important and, understandably, the military were the most interested in revaccination A standardized programme of vaccination of civilians was not yet in force in Germany England also had difficulties in adopting vaccination regulations Polls were held among governments and physicians and it appeared that the transmission of syphilis was thought to be a great disadvantage, it had

The Englishman Jenner, born on May 17, 1749, knew nothing of these cases. In his youth he had heard from the wife of a farmer that having had cowpox had made her immune to smallpox. This led him to begin in 1775 a series of experiments which led to the use of human cowpox lymph for vaccination. On May 14, 1796, the lymph was taken from milkmaid Sarah Nelms and administered to 8-year-old James Phipps. A later inoculation of this boy with variola produced no effect. Jenner's service was mainly in his prolonged series of experiments stemming from a folktale and his discovery of the vaccination with human lymph. This discovery made it possible to distribute the vaccine. The result of all this work was that in the beginning of the 19th century vaccination laws were passed in several European countries, beginning with the domains Piombino and Lucca, which had been established by Napoleon and were ruled by his brother-in-law. Vaccination also gained acceptance in countries outside Europe and ships carried human lymph from vaccinated children to other parts of the world (The Phillippines, Peru, etc). Special church services were held to welcome those who brought the lymph. The church was even the site for the vaccination In the United States the first vaccination was performed on May 8, 1808, using vaccine from England. Benjamine Waterhouse performed the vaccination on his own son after having read Jenner's reports (The antagonism which he stirred up by this act made it necessary for him to resign from his position as professor at Harvard University in 1810)

In opposition to this enthusiasm, there arose antivaccination movements, and, in addition, there were many (among them Jenner) who warned against too great optimism Many of those who protested had already practised inoculation. Their warnings about 'Verviehung' now seem comical a vaccinated child became four-footed, another mooed like a cow and yet another coughed like a calf or developed hair over its entire body! However, the warnings concerning failures in the vaccination were more authentic; it appeared that the lymph was often used without proper foresight, mistakes and carelessness were common, laymen administered vaccinations. Consequently, the results of vaccination fell far short of expectations. This proved to be the case in England when, during smallpox epidem-

ics, vaccinated people also fell ill; this did great harm to the reputation of vaccination. The fanatics defended themselves by placing the blame on the use of 'bastard vaccine', but found even better support in the fact that the mortality in the case of vaccinated patients was considerably lower than in the unvaccinated. This is to be seen in the following statistics from the Stockwell Smallpox Hospital, London.

Patients	*Scars*	*Fatalities*
703	none	47.5%
516	one poor	25 0%
632	one good	5 3%
677	two good	4 1%
301	three good	2.3%
259	four or more	1.1%

But this evidence was rejected on the grounds that the vaccinated patients were not recognized as smallpox patients.

In this battle, neither of the two sides made a systematic study of the problem Another question was whether the acquired immunity of a vaccination would last a life-time or would disappear after a number of years Inasmuch as the facts seemed to point towards the latter, Pearson advised revaccination. This was no discredit to vaccination for there were cases of people having had smallpox twice, and why should the immunity of a vaccination not decrease with time?

Two things were clear from all of these facts: (1) it was possible to contract smallpox after vaccination, even though it was generally in a milder form (varioloid); (2) acquired immunity was temporary

Since the danger of smallpox was (and still is) very great in armies the first revaccinations were performed on German military personnel. While previously smallpox had been predominantly a disease of children, the use of vaccination made the second and third decennia the most important and, understandably, the military were the most interested in revaccination A standardized programme of vaccination of civilians was not yet in force in Germany. England also had difficulties in adopting vaccination regulations. Polls were held among governments and physicians and it appeared that the transmission of syphilis was thought to be a great disadvantage, it had

already occurred that spirochetes were transmitted with the smallpox material. During the 1860's another solution was sought and the possibility of using animal lymph was considered. The state of vaccination was rather poor. Epidemics continued to break out and in 1870 (war!) a veritable explosion of smallpox occurred as a result of the increased movement of the civilian population as well as military personnel. Exact statistics from this time do not exist, but it is thought that the mortality among the unvaccinated was between 30 and 70%. In the case of vaccinated patients, the morbidity and mortality were much lower. This led to the passing, on April 1, 1875, of a vaccination and revaccination law for the whole of Germany Originally, use was made of both animal and human lymph but because of the danger of the transmission of syphilis an investigation was carried out by Robert Koch, which led to the use of animal lymph only.

This progress continued until almost all countries had regulations governing vaccination. In the 1930's Europe presented the following picture concerning vaccination:-

France: mandatory vaccination before the age of one year, revaccination at the ages of 11 and 21. These regulations were very important because of the close contact with North Africa.

Great Britain vaccination was performed under the age of two, but parents were allowed to refuse on religious grounds. The vaccination picture varied from place to place, but was certainly not optimal

Russia. had the same rules as France· three obligatory vaccinations

Italy· three periods during which vaccination was compulsory. 0–6 months, at school age, and during military service.

Germany had the best vaccination regulations. Here too there were certain periods of compulsory vaccinnation· under the age of one, at the age of 12 for schoolchildren, and during military service.

The regulations in the smaller countries have not been mentioned but generally follow the pattern of the rest.

At present there are still national differences In Great Britain, there is still a considerable number of unvaccinated persons· these are generally so because of religious convictions. The rather frequent occurrence of cerebral complications of vaccination must also play a part here Turnbull was the first, in 1912, to recognize the clinical

picture of post-vaccinal encephalitis. In the 20's he wrote a report to the Minister but, before his findings were released to the public, Van Bouwdijk Bastiaanse had had his first report published. This led, in Great Britain as well as in the Netherlands, to the establishment of an Encephalitis Committee.

In France, even at present, the vaccination situation is more satisfactory; nevertheless, it is not ideal In 1954 there was an eruption of smallpox at Vannes in which a large number of unvaccinated patients, doctors and nurses were infected.

In 1946 Great Britain stopped all regulation of vaccination.

Through the great increase within the last decennia of continental and inter-continental traffic, the importance of vaccination regulations has assumed an international rather than a national character. We believe that, because of certain affective reactions to vaccination, the Netherlands occupy a more or less unique position in the world picture, as will be explained in the next chapter.

DEVELOPMENT OF THE VACCINATION PROBLEM IN THE NETHERLANDS

As was mentioned at the end of the last chapter, the Netherlands have been, and remain, in an unusual situation with regard to the problem of vaccination. While the arguments against vaccination in other countries were principally medical, those in our country were mainly of a theological or political nature. The Dutch tend to theologize. With this background of theology the problem of vaccination became so affect-loaded that it was often impossible to obtain an objective, sober analysis or judgement. The objections to vaccination have usually been voiced by members of the orthodox Protestant groups. These groups held the opinion that everything that happened was God's Will, and that if He ordained that we should fall ill it was not proper that we should attempt to thwart the illness by taking precautions such as vaccination They also quoted from the Bible saying that a healthy man needs no physician (see below) It is easily understood that such a point of view can lead to serious consequences The situation became even more complex when religion and politics became linked by the establishment of political parties with religious foundations This resulted in the colouring of parliamentary debates by the religious convictions of the various groups. In order to understand fully the difficulties which surrounded the problem of vaccination regulations, we must always bear in mind the theological-political situation

The physician Abraham Capadose was closely involved in the development of the problems concerned with vaccination. This physician, who had become converted from Judaism to Christianity, considered vaccination as he did magnetism He was among those who reasoned from Luke 5 31 " they that are whole need not a physician " Further, reasoned Capadose, the number of deaths within a certain period was predetermined, and those lives which might

be saved by vaccination would certainly be lost by other means! For a physician, a dangerous point of view! Capadose taught his followers that the ability to heal was a great gift but that one should not attempt to prevent disease because in doing so one tries to be greater than one's Creator, who called Himself merely a healer.

There were some in the camp of the vaccination adherents who performed, often reprehensible, experiments, frequently on foundlings and orphans. Capadose used these as the basis for his attacks on vaccination, and not without reason. But when he states that because of the vaccination the children look miserable and that the human race suffers because the normal development is disturbed, it becomes difficult for a present-day physician to follow him It becomes more difficult when, after making the above statement, he later comes to the conclusion that no effect can be expected from vaccination since susceptibility to disease is a result of the Fall from grace and, therefore, unalterable.

Nevertheless, the influence of Capadose was considerable. Remarks of some politicians are in the same vein. Keuchenius, at the time one of the leaders of the Anti-Revolutionary Party said: "The Gospel is God's path towards salvation the vaccine is Jenner's way towards purification and health of the cow. Instead of the eternal Gospel of God's grace in Christ, the enlightened of this century have found a new Gospel, that of Jenner's cow's love for mankind, which speaks of sin and redemption, but the sin is only by smallpox, and the redemption, only from the taint of pox "

Having indicated the atmosphere surrounding the vaccination question, we should like to follow the development of vaccination regulations in the Netherlands The translation of Jenner's work in 1801 was a signal for many to intensify their fight against vaccination. Prior to this, when only the inoculation method was used, there might only be carried out with the consent of the 'Magistrate' and only at times when small-pox had been diagnosed in that locality

By 1825, vaccination had practically replaced inoculation with small-pox virus, so that the battle was concerned solely with vaccination

This battle was not in the beginning an official one (see above).

Under the influence of the development of vaccination regulations in other countries it probably became increasingly clear that something along these lines was needed in the Netherlands.

On December 4th, 1872, under the guidance of Minister Thorbecke, the first vaccination law became a fact. Vaccination was declared compulsory for pupils and teachers in primary schools, for volunteers in charitable institutions, prisons and for Army and Navy personnel.

In some places pro-vaccination propaganda took the form of premiums, etc. In spite of the protests from those whose religious and moral principles were in conflict with vaccination, the law remained in force until 1929.

This is not to say that there were not many attempts to change the course of events, among others by the proposed law of 1903 (Kuyper). This was intended to reduce the number of children absent from school because of non-compliance with the law of 1872 by making it possible to receive a certificate of exemption from vaccination because of *religious convictions. This was to be coupled with a declaration that* the person was not insured against the effects of a disaster (fire, storm, etc.).

These certificates were to be requested orally from the Mayor in the presence of two witnesses. The exemption was valid for one year. At the same time it was strongly advised that school personnel and children above the age of eleven should be revaccinated. The above became law on July 17th, 1911.

In 1924 a new law was proposed by Aalberse, suggesting that denominational and non-denominational schools be treated alike, that the validity of exemptions be extended to three years, and that the requirement of two witnesses be replaced by the swearing of an oath. This law was never passed owing to the change of Ministries in 1925.

Meanwhile, the first reports of post-vaccinial encephalitis had been published (Van Bouwdijk Bastiaanse *et al.*). This gave rise to a new problem. Laymen and physicians *alike became hesitant and this* resulted in the law valid at that time becoming completely ineffectual.

In February, 1927, the Ministers proclaimed that the proposed *changes exceeded the limits set by the Cabinet*. This fixed the situation

of vaccination at the 1872 level, but it was not to remain there for long. On March 9th, Bijleveld proposed an amendment granting exemption from vaccination on the ground of conflicting principles, and with terms similar to those suggested by Aalberse but with the following changes: The exemption would be permanent and the limitation on the total number of exemptions would be eliminated. The revaccination regulations were to remain unchanged.

The amendment was defeated, changed and re-submitted in its new form. After fierce opposition the amendment was passed on June 8th, 1927.

In February, 1928, enforcement of the indirect compulsion was postponed until January 1st, 1930, and because of the threat of post-vaccinial encephalitis repeatedly postponed, each time for the period of one year.

In 1938 a committee (the second) was formed to investigate whether the law of 1928 should be enforced or changed and, if changed, in what manner. This led to the drawing up of a new law which was passed on December 22nd, 1939, and became effective as of January 1st, 1940. This law stated that all children should be vaccinated before reaching the age of one year. The parents would be warned by the Mayor of their community when a child reached the age of four months. Exemptions were to be obtainable on application; a physician had to be consulted and the reasons, medical and otherwise, given. The penalty for failure to comply with this order was a term of imprisonment and a maximum fine of 100 guilders. Thus, this law utilized the means of individual legal persuasion. The result has been that since that time the majority of the inhabitants of the Netherlands have been vaccinated between the ages of six and twelve months.

A weak spot in our vaccination condition arose in the years preceding 1939: parents did not have their children vaccinated, and physicians, recognizing the risks involved, hesitated to take the initiative. As a result, a considerable group of persons now aged 20-35 years have never been vaccinated.

Since it is largely from this age group that both the military recruits and emigrants come, the risk involved in vaccination (in this case primary vaccination) was considerably increased, a fact that is reflected in the statistics of the last few years.

TABLE 1 NUMBER OF CASES OF AND FATALITIES FROM VARIOLA MAJOR (VARIOLA MINOR) IN ADDITION TO THE NUMBER VACCINATED AGAINST SMALLPOX SINCE 1900

Year	Number of cases variola major (variola minor) Cases	Death	Total number of vaccinations	Per 1000 inhabitants	Number of children of 0–5 years	Number of vaccinations of children of 0–5 years	Per 1000 children of 0–5 years
1900	68	6	129021	25.27	786938	118308	150.34
1901	40	8	127217	24.56	794787	116473	146 55
1902	56	5	142189	26 57	804097	115615	143 78
1903	150	22	137500	25.74	813918	119825	147.22
1904	106	12	130159	23 80	824306	119458	144 92
1905	64	13	133357	24.03	835136	120983	144 87
1906	43	6	154749	27.47	847049	136419	161.05
1907	43	6	135387	23 71	858248	124742	145 34
1908	7	1	138634	23.96	864961	127579	147.50
1909	17	—	140589	23 99	871576	129242	148 29
1910	7	—	143836	24 37	879344	133703	152 05
1911	4	—	142213	23 76	880785	131551	149 36
1912	8	1	142913	23.55	884168	131660	148 91
1913	37	4	185423	30.08	893726	138499	154 97
1914	2	1	161665	26 02	903670	137631	152.30
1915	7	1	153465	24 00	909566	137244	150 89
1916	85	8	163402	25 08	914189	141672	154 97
1917	—	—	138645	20 87	923787	125627	135 99
1918	—	—	142728	21.29	922993	131787	142.78
1919	5	—	147128	21 59	911029	134441	147.57
1920	50	3	149392	21.95	914573	133991	146 51
1921	—	—	140949	20.20	935758	127467	136 22
1922	—	—	145370	20 51	955349	132580	138.78
1923	—	—	159063	22 25	974523	145927	149 74
1924	—	—	162328	22.35	998008	149646	149.94
1925	2	—	165386	22 48	1018629	153028	150 23
1926	3	1	174847	23 71	1021838	157412	154 05
1927	—	—	150653	20.01	1011881	140414	138.77
1928	—	—	52757	6 92	1007409	49875	49 51
1929	2(449)	21	1469914	190.14	1003340	104140	103 83
1930	—	—	27131	3 46	999830	25417	25 42
1931	1	—	28528	3 60	1000723	26667	26 64
1932	—	—	26338	3 27	1003035	24416	24 34
1933	—	—	25096	3 07	1004353	22899	22 80
1934	—	—	21940	2.63	1001830	19132	19 10

Year	Number of cases variola major (variola minor)		Total number of vaccinations	Per 1000 inhabitants	Number of children of 0–5 years	Number of vaccinations of children of 0–5 years	Per 1000 children of 0–5 years
	Cases	Death					
1935	—	—	17682	2.09	997882	15069	15 10
1936	—	—	21061	2.48	992868	18162	18.29
1937	—	—	25485	2.95	987584	21630	21 90
1938	—	—	30969	3.56	986096	28272	28.76
1939	—	—	40984	4 67	992696	37638	37.91
1940	—	—	61840	6.98	148846 [1])	48327 [1])	324 68
1941	—	—	94058	10 49	181959	80996	445 13
1942	—	—	92846	10 31	189975	87689	456 74
1943	—	1	88148	9 69	209379	85623	408.90
1944	—	—	Because of the war, figures are not reliable.				
1945	—	—					
1946	—	—	79988	8 49	284456	75437	265 20
1947	—	—	174158	18 09	267348	135130	505 45
1948	—	—	155699	15 89	247923	150774	607 06
1949	—	—	220122	22 11	236177	171572	726 99
1950	—	—	109730 [2])	10.85 [2])	229369	107299 [2])	467 80 [2])
1951	52	2	641379 [2])	62 49 [2])	228631	145858 [2])	638 00 [2])
1952	—	—	144829 [2])	13 95 [2])	232557	141540 [2])	608 62 [2])

[1]) In connection with the vaccination law of 1939, the figures for the years following 1939 refer to the number of live births and to the number of vaccinations performed under the age of 2 years

[2]) Provisional statistics

In addition to the above-mentioned circumstances, the danger of an insufficiently vaccinated population was demonstrated when it became necessary to perform mass vaccination in the southern part of our country because that area was exposed to the very real threat of an epidemic. This applies particularly to Tilburg

Fortunately, vaccination has been gaining ground in the Netherlands (*cf.* Table 1) We are becoming convinced that vaccination of an entire population must not be neglected, especially in view of the recent threats (1947 and 1951 in Tilburg, 1953–54 in The Hague)

Nevertheless, the problem of post-vaccinial complications of the central nervous system remains And this is a very real danger! In 1954 compulsory vaccination of recruits became law. Those refusing

an unvaccinated person. In our Out-Patient Department, we sa\ child with post-vaccinial encephalitis who had transmitted the vacc to her mother, with the result that the latter contracted a vacci generalisata. After this, a condition developed which we shall cal 'diencephalosis' (Sillevis Smitt) This is probably a case of a cereb reaction to a vaccinia infection.

(B) Eczema vaccinatum: This can be caused by (unwisely) vaccinat a child suffering from eczema, or by infection of the child through means discussed under (A).

(C) Neuralgia: especially after revaccination (Wayenburg, \ Bouwdijk Bastiaanse).

(D) Vaccinia: generalized syndrome such as we also see with ot contagious diseases and which appears during the development of pox-pustules. See Chapter 4 (Sissingh)

(E) Convulsions in children· Report of the Netherlands Society the Advancement of Medicine.

(F) Increased fetal mortality in the second and third months pregnancy

The possibility of this was established by MacArthur in 1952 duri an investigation concerning the effect on fetal mortality of vaccinatic This raises the question whether there is trans-placental infection the fetus, it is more or less to be expected considering its occurren in other virus diseases such as German measles Greenberg and othe on the other hand, believe that there is no connection between vaccir tion during pregnancy and increased fetal mortality.

(G) Glomerulonephritis after vaccination· Recently, Koster h brought forth new evidence concerning this danger. He advises agair the vaccination of cases of chronic nephritis because of the danger acute exacerbations The author has seen a case of post-vaccini encephalitis which was concomitant with a nephritis

(H) Vaccinia generalisata the development of pustules all over t body

(I) Vaccination exanthema· this exanthema, seen following a vaccin tion, exhibits great variation it can look like measles, scarlet feve or even erythema exudativum multiforme

Most of the above skin changes develop approximately one wee after vaccination, therefore at about the same time as the pustu

reaches its maximum development. In addition, there are other skin conditions which occur later and are seen especially after revaccination Here the incubation period varies between 16 and 21 days. We can differentiate between two groups (Malie *et al.*):

(1) Very diffuse papulovesicular exanthema In addition to forms which are primarily papular, we also see vesicular forms, and others consisting of very small papules.

(2) Solitary erythemato-vesicular spots which correspond with 'Exanthèmes fixes'.

These conditions generally disappear spontaneously. No virus or other pathogenic organism has yet been isolated The possibility of an allergic reaction must be considered.

(J) On rare occasions we may see a haemorrhagic diathesis, with bleeding into the skin, mucosae, and even kidneys. Similar conditions are also seen in other virus diseases (Veldkamp, Keyzer).

(K) Positive Wassermann reaction following vaccination: this was originally described by Bellow *et al*, and more recently confirmed by Winser)

(III) *Late complications*

(A) Post-vaccinial pustules. occasionally, a second set of pustules appears 4 or 5 weeks after the vaccination, thus after the healing of the first set.

(B) Keloid formation in the scar this is very resistant to therapy; we often see recurrence even after wide excision

(C) Post-vaccinial encephalo-myelitis This important complication will now be considered

The first step we took was to separate the encephalitides after revaccination. The total of the dates after primary vaccination is represented in Fig. 2.

We see here a peak at 7 and one at 12 days. This could mean that we are dealing with a curve that is an expression of two factors, *i.e.* the incubation period for young children and the incubation period for older children and adults. If we separate these results into two groups, one under two years (where we see clinically very little post-vaccinial encephalitis) and one above two years, we obtain the picture represented in Fig 3.

We see that both diagrams tend to follow a regular curve. The first diagram shows a peak at 12–13 days, which is the incubation period that is generally seen in post-vaccinial encephalitis The second shows a peak at 7 days but also shows a more irregular picture and the spread is large.

Our findings have been checked by the Statistics Department of the T N O by means of Student's *t* test The average incubation period of cases of post-vaccinial encephalitis in children over the age of two was 11 57 days In the group from 0–2 years it was 9 days. The difference between the averages (2.57 days) is very strongly significant ($P \leqslant 0\ 0001$) In addition, it appeared that the spread of incubation periods in the two groups was significantly different; it was much greater in the 0–2 group than in the group over two ($P = 0\ 03$) The standard deviations were found to be respectively 3.4 and 2 6 days

Although the *t* test can theoretically only be used if the spreading *within both groups is the same, the statistician believes the significance* of the difference between the two averages to be so great that the difference in spread within the groups has no influence on the conclusion

Since some believe that post-vaccinial encephalitis in young children is based on a chance coincidence of a vaccination and an encephalitis, we had our statistics examined as to the probability of such an occurrence If it were true that the chance of encephalitis was independent of the time, *i.e.*, that this chance was equally great for every child every day, then we should (if indeed the occurrence of encephalitis had nothing to do with vaccination) expect to see a regular (rectangular) distribution Bucking, through the use of the (1 × 5)

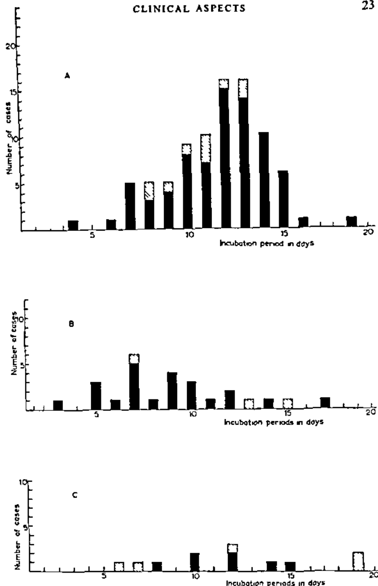


Fig 3 (A), Cases over 2 years of age, (B), Cases under 2 years of age; (C) Cases after revaccination

table showed, however, that there was a significant deviation ($P = 0.001$) from the rectangular distribution. There must therefore be a relationship between the vaccination and the encephalitides which follow them Exactly what this relationship is must be further investigated.

The onset of the disease is generally acute or subacute. One often finds that during the development of the pox pustule the patient goes through a period where he feels sick and has a high temperature, with or without cephalalgia. This is the picture of the vaccinia. One or more days later the disease symptoms can break out again, this time more abruptly; these are the first symptoms of post-vaccinial encephalitis. The most striking symptoms in the beginning are:

(1) Fever. Often extremely high.

(2) Mental confusion. The intensity varies from patient to patient, not only as an early symptom but also during the course of the disease, and ranges from slight disturbances in the level of consciousness where the patient exhibits amentia, to cases where patients are in a coma

(3) Headache. This is generally throughout the whole head, especially in the occipital region. Often there is vomiting and signs of meningeal stimulation, *e.g* rigidity of the neck, sign of Kernig, Brudzinsky

(4) Convulsions. Seen especially in children in the early stages but occasionally in adults also.

Very young children often have lengthy spasms of their extremities with or without trismus With this general syndrome we also see other symptoms that have a focal character. In a large group of cases there are signs that point to pyramid tract involvement. We can find uni- or bi-lateral pathological reflexes with or without paretic symptoms Symptoms pointing to involvement of the extra-pyramid system are seen occasionally.

In 1954 we saw a patient with post-vaccinial encephalitis who did not show any paresis but who was unable to perform the finger-nose test correctly The movement was one between a cerebellar ataxia and a rough tremor such as is seen in damage of the basal ganglions. In the arms there was cogwheel rigidity

The cranial nerves may be affected, the motor-cranial nerves usually being the most involved

In the group of families that we investigated we found a probable abortive case that expressed itself two weeks after vaccination by ocular muscle paresis (musc.rect ext) Occasionally during the course of the disease optic nerve neuritis was observed An almost constant symptom is micturition disturbance: incontinence as well as retention. Sometimes signs of medulla oblongata involvement are seen; these include disturbances of respiration, swallowing and speech

Investigators who describe hyperalgesia point out the possibility of spinal nerve involvement. This is usually in the background, however, and does not serve as an important diagnostic aid.

In addition to the lowered level of consciousness, there are other psychic symptoms We have, for instance, noticed (patient p. 75) a negativism. This has been described by other investigators Delirium and agrypnia appeared occasionally.

The laboratory findings of patients with post-vaccinial encephalitis vary widely. The blood sedimentation rate can be greatly increased but is often normal The cerebrospinal fluid shows changes that vary from one patient to the other One patient may have a normal cell value and another patient definite pathological changes in regard to cells The cell reaction varies from a slightly to a greatly increased number of lymphocytes The protein content of the cerebrospinal fluid is very often raised, extreme readings, however, are seldom seen The Mastix-sol and Gold curves are often pathological The changes are usually in the first part of the curve, resembling changes seen when there is rapid destruction of parenchyma The sugar content of the cerebrospinal fluid is a point of discussion Sometimes in post-vaccinial encephalitis we find an increased sugar content but usually the findings are normal There is little support for the theory that the sugar level must be pathological, as in the cases of epidemic encephalitis

After looking at the complete picture we can conclude that in post-vaccinial encephalitis it is the cerebral symptoms that dominate, with minor changes taking place in the myelum

Occasionally the myelum changes dominate the picture In 1952 we saw a young man of 20 who, 12 days after vaccination, showed syndrome of a transverse lesion of the spinal cord After several months the condition cleared up without leaving any trace The case

was diagnosed as post-vaccinial transverse myelitis at the level of D IV.

Changes in the peripheral nervous system (neuralgia, peripheral paralysis) are seldom described in the literature. Neuralgia has been observed after re-vaccination (Van Wayenburg, Turnbull, *Report of the Encephalitis Commission, 1932*, Sillevis Smitt, Meunier, Van Bogaert). Uiberall has described two cases of post-vaccinial polyneuritis during the vaccination of the population of Santiago di Chili.

The course of post-vaccinial encephalitis varies. In the literature, therefore, one finds varying figures as regards mortality. Before the second world war the following figures were given (after Meunier).

Tyrol 71.4%	Belgium 31.6%
Netherlands 31%	Germany 35%
England 40%	

In 1947 Keyzer reported the epidemic in Tilburg as having a mortality of 2 per 27 patients.

The course of the disease is usually two weeks. Sometimes the disease lasts but a few hours. These quick and usually serious cases often end fatally.

In the course of time the medical world began to accept the fact that post-vaccinial encephalitis ended in one of two ways; either death or recovery without any trace of the disease. Sillevis Smitt and Biemond, however, pointed out that recovery could occur with permanent damage to the nervous system. In carrying out our family investigation we inquired as to permanent damage. The findings were as follows

Complete recovery. 48 patients.
Fatalities. 23 patients
Incomplete recovery 38 patients
3/46 Institutionalized for epilepsy. Imbecile.
7/46 Epilepsy for two years following vaccination
2/47 Personality changes.
5/47 Cephalalgia
6/47 Personality changes
16/47 Personality changes. Intolerance for alcohol
19/47 Incontinentia urinae. Irritable. Right-sided paresis. Pathological reflexes.
(20/47 Patient's brother developed a strabismus following vaccination.)

21/47	Derealization Incontinentia urinae. } Same family.
22/47	Incontinentia urinae }
27/47	Right leg paretic Right and left foot-sole reflexes with dorsal flexion
29/47	Cephalalgia.
37/47	Incontinentia urinae. Walks with difficulty (anamnestic)
43/47	Cephalalgia Has become very nervous. Cousin of 42/47.
44/47	Left foot-sole reflex: dorsal flexion
53/47	Cephalalgia
59/47	Incontinentia alvi et urinae
64/47	Patellar reflex more active right than left Left foot-sole reflex dorsal flexion.
1/48	Right hemiparesis Motor aphasia and alexia.
2/48	Mentally retarded.
8/48	Malaise in the afternoons
10/48	Epilepsy Plantar reflexes dorsal flexion.
15/48	Cephalalgia Attacks similar to Menière
17/48	Plantar reflexes: right, dorsal flexion, left, uncertain
18/48	Easily tired Pain in left arm. Strabismus
12/49	Mentally retarded
14/49	Right plantar reflex, dubious dorsal flexion
2/50	Ataxia Epilepsy Right facial paresis
1/51	Cephalalgia Disturbed power of concentration
2/51	Spastic paraparesis of legs and paresis of left arm Scapulae alatae
4/51	Greatly increased need for sleep
15/51	Cephalalgia
19/51	Cephalalgia
22/51	Slight encephalopathic syndrome
31/51	Cephalalgia Depressive
36/51	Cephalalgia
45/51	Cephalalgia
54/51	Encephalopathic syndrome with pathological rage
59/51	Cephalalgia.

(This table shows almost the same relations as found by Puntigam and Berger, 1956).

An important point is the question of recurrences This was mentioned in the '1932 Report' and later described by other writers (Rigotti, Hausmann) In connection with the etiology (compared with the 'Schube' in multiple sclerosis) we consider it undesirable to neglect this point

To the question What are the chances of getting post-vaccinia

encephalo-myelitis after vaccination? we find ourselves unable to give a clear-cut answer owing to the great variety of statistics.

In the Netherlands during the years 1924–1934, there was one case per 22,000 vaccinations in one- and two-year-old patients. Mortality was 0. Amongst the rest of the population there was one case per 3,600 vaccinations. For every 13,000 vaccinations one death was recorded. These figures are stated simply to give the reader an idea as to the frequency of the disease; the figures have little value further. There are patients regularly attending our Neurological Out-Patients Department with symptoms that can be regarded as symptoms of previous post-vaccinial encephalitis. In many cases the diagnosis is made at the clinic for the first time. Therefore these are cases that have never found their way into the statistics. Even if the diagnosis had been made earlier we have no assurance that the case was registered with the Chief Medical Officer. This appeared not so very long ago in an article concerning a number of cases in which the diagnosis of post-vaccinial encephalo-myelitis was probably certain. On further investigation, the Chief Medical Officer appeared to know nothing concerning these cases If we are to become better oriented in the prevention of this syndrome, case reports will have to be more complete Perhaps we can get a clearer picture of the incidence by reporting the results of the mass vaccination at Tilburg.

1,206 children of 0–6 years were vaccinated without a single case of post-vaccinial encephalitis resulting Following 14,792 vaccinations of children from 7–17 years old, there were 27 cases in which the diagnosis of post-vaccinial encephalitis was practically certain, which means that there was one case per 650 vaccinations (primary and revaccination together), which was to be expected (Terburgh) No cases of post-vaccinial encephalitis were observed following the vaccination of 758 persons older than 18 Nevertheless, the total number of encephalitides was rather large, comparable only with the 1944–45 results of vaccinations in Basel, Switzerland, where there was a morbidity of 1–2%.

The Medical Officer (1952, p 161) reported 31 cases in five million vaccinations, 13 of which were fatal.

Of 750,000 vaccinations in Glasgow and Edinburgh in 1943 there were 18 cases, 4 of which were fatal

In 1950 there were no new cases seen in 162,000 vaccinations The same holds for Brighton, where 90,000 vaccinations were performed.

The question whether post-vaccinal encephalitis is encountered in children under the age of one year has received and continues to receive much attention We need only refer to articles by Julius and by Peters and Neurdenburg. Clinically, there have certainly been cases in which the diagnosis has been justified That the picture is very much altered when the patient is a very young child may be seen in the different incubation periods and from the pathological anatomy, which we shall discuss presently Another very important question is that of the post-revaccinial encephalitis, which does occur, although much less frequently (Van Bouwdijk Bastiaanse) The morbidity of encephalitis after revaccination lies in the neighbourhood of 1:50,000

The *Report of the Encephalitis Commission, 1932* mentions 26 cases occurring after revaccination. The cutaneous reaction was accelerated in seven cases The interval between primary vaccination and revaccination varied from 14 to 40 years, while the oldest patient was a man of 76 The mortality was 26.9%. We have already mentioned the occurrence of neuralgiform pain after revaccination According to correspondence from other authors and our own experience in the Utrecht clinic, this also occurs following primary vaccination The statistics published several years ago in Austria agree, to a large extent, with the above For more information concerning post-revaccinial encephalitis see Chapter 5

After reading the above sketch of the many possibilities involved, it will become clear to the reader that the warnings at the beginning of this chapter were not without foundation.

We can trace the following series of post-vaccination events. The development of the pustules may be accompanied by fever, which may be extreme. The cephalalgia with or without signs of meningeal irritation and the lowering of the level of consciousness that often accompany the fever make it difficult to differentiate between 'vaccinia' and post-vaccinial encephalitis. In 1949, Sissingh found that of 570 vaccinations 119 people were found to have suffered from vaccinia, for an average of 4 days, and were unable to work

We often see the same picture in other infectious diseases Cornelia de Lange (1943) mentions the frequent occurrence of these symptoms

in measles. They are so common in typhoid fever that they form an important aspect of the clinical picture Histologically, these conditions are characterized by a slight meningeal exudate (meningitis serosa) and a few lymphocytes around the parenchymal vessels (De Vries) The difficulties of the differential diagnosis have stimulated a few workers to attempt to clarify the situation. Baumann suggested dividing the clinical pictures as follows:

(A) *Morbus postvaccinalis per se. Here we see only general symptoms;* there are no neurological or psychiatric changes.

(B) Encephalopathia postvaccinalis. General neuropsychiatric symptoms without any signs of cerebral damage.

(C) Encephalitis postvaccinalis. Neurological and/or cerebrospinal fluid changes.

This classification does not help us towards an easier and sharper *differential diagnosis. Should we classify a case of high fever plus* slight lowering of the level of consciousness under (A) or under (B)? Obviously, these are symptoms of an infectious disease and, as such, fall under (A), but if we consider the psychiatric aspect (the lowering of the level of consciousness) they can also be classified under (B) In addition, what exactly are we to understand by "general neuropsychiatric symptoms"?

In 1932 the Encephalitis Commission attempted to set up a more practicable classification based on clinical findings plus any available pathological-anatomical evidence. It distinguished:

(I) Cases which, on the basis of the available evidence, could be considered as being definitely post-vaccinial encephalitis.

(II) Somewhat doubtful cases which were in all probability post-vaccinial encephalitis

(III) *Doubtful cases in which it was just as probable that they were* not post-vaccinial encephalitis as that they were.

(IV) Cases concerning which little more was known other than that vaccination was followed by illness or death, and where case reports were incomplete The commission did not think it justified to disregard these cases completely if the period between vaccination and illness or death seemed to indicate a connection

This classification is also far from perfect, especially when we consider that the pathological anatomy must also be taken into

account. Thus we see cerebral complications following vaccination which fall clinically more or less under the above classification, but which are anatomically quite different. Since we are never aware of the pathological-anatomical picture at the bedside we might do well to ask whether it is even possible to make the diagnosis of post-vaccinial encephalitis with certainty.

The pathological-anatomical changes which we shall discuss presently and which have been so often described as classical (i.e. the perivenous demyelinating microglia encephalitis) must always be considered in addition to the clinical course. It is our opinion that by the diagnosis 'post-vaccinial encephalitis' is meant the post-vaccinial appearance of cerebral reactions which may be of infectious nature.

In the majority of the cases and especially if the incubation period agrees with that outlined above, this reaction will be definitely connected with a vaccination and the anatomical changes will agree with the classical picture of the microglia encephalitis.

We must, however, make some reservations for the other possibilities.

PATHOLOGICAL ANATOMY

We have been very fortunate in that, since 1925, the pathological-anatomical investigation of cases of post-vaccinial encephalitis in the Netherlands has been largely carried out at the Utrecht Neurological Clinic (Van Bouwdijk Bastiaanse, L. Bouman, De Vries); this has led to the collection of a vast amount of material. Here we have come into close contact with the many problems concerning the anatomical background of this condition.

Is there a specific histological picture to be seen in all cases in which the clinical diagnosis of post-vaccinial encephalitis has been made? In other words, is the more or less typical clinical picture accompanied by a specific anatomical background? Originally, this was thought to be so. A series of investigators, many of them Dutch (Van Bouwdijk Bastiaanse, Cornelia de Lange, Brouwer, Sillevis Smitt, Bouman, Bok, and others), described the picture which De Vries called, 'peri-venous demyelinizing microglia encephalitis' (abbreviated: 'microglia encephalitis'). This was thought to be specific. In this condition, very diffuse peri-venous or sometimes peri-arterial (but never peri-capillary) masses of microglia cells are to be seen in the parenchyma (Fig. 4), and these microglial collections generally show more or less diffuse demyelinization (Fig. 5 and 6). Small collections of lymphocytes and mononuclear cells may also be present in the Virchow-Robin spaces (Perdrau, Cornelia de Lange, Van Gehuchten and Falcon). The axons in these areas of demyelinization remain largely intact, so that there is a discrepancy between the condition of the axons and the related myelin sheaths. Also noteworthy is the fact that the ganglion cells in these areas are completely unaffected. This may be significant in considering the etiology (De Vries, Kokken), which will be discussed in a separate chapter.

This demyelinization and microglial growth may also be sub-ependymal and sub-pial, the so-called 'edge gliosis' (Wohlwill, C. de Lange, De Vries) seen with a slight meningeal reaction (Fig. 7).

In the spinal cord, increases of glia can be observed along the radiations of the posterior roots, the efferent veins, and the afferent arteries. The affected areas of the cerebrum as well as the cerebellum are generally localized in the white matter, hence the inclusion of the condition under the group 'leuco-encephalitis' (Pette). This localization in the white matter becomes less and less clear the more caudally one makes sections (Van Bouwdijk Bastiaanse, Turnbull and Mc-Intosh, Pette, Leiffer, Oesch, Finley and others). This means that in the brain stem (thalamic nuclei, globus pallidus, nucleus caudatus, substantia nigra) and in the spinal cord we shall find affected areas in the grey matter. Here, there is very often a neuronophagia (De Vries, Van Bouwdijk Bastiaanse, Querido, Wiersma). Suppan reported that the incidence of localizations in the mid-brain and surrounding the fourth ventricle is higher in children under the age of 5 than in adults. Perdrau described early lymphocytic and plasma cell infiltration of the spinal ganglia. This changing of the histological picture at different levels is not an isolated phenomenon: in acute anterior poliomyelitis we often see that the bulbar reactions are more benign and transient (the localization is more dangerous!) than the spinal ones.

The meningeal reaction shows itself as an infiltration of lymphocytes and large mononuclear cells; we never see plasma cells. The vascular reactions and haemorrhages are of an unknown nature (Lumsden, Van Gehuchten, Falcon). The parenchyma is normal around the infected areas, *i.e.* there is neither a diffuse oligoglial increase nor an infiltration about the small vessels.

According to De Vries the histological picture in the affected areas is fully developed by the 11th day after vaccination, regardless of the duration of the clinical symptoms. In cases of longer duration, the areas may become confluent through a more diffuse microglial perivascular infiltration, which means that the greatest degree of infiltration was not immediately around the vessel. In addition, we may see fat-granule cells in areas of greater necrosis.

We should now like to consider the problem already mentioned of the connection of the clinical picture with the anatomical background

called by De Vries: peri-venous demyelinating microglial encephalitis. In 1939, Comby pointed out the various reaction patterns of the nervous system following vaccination, and Hans Jacob, in 1948, emphasized them further. In 1950, in an article entitled "Post-infectious encephalo-myelitis and multiple sclerosis", Ludo van Bogaert described several possibilities of cerebral reaction following infectious diseases. In addition to the peri-venous encephalitis, he differentiated: (1) non-suppurative lymphocytic meningo-encephalitis, and (2) haemorrhagic pseudo-encephalitis.

Constitutional factors were considered to decide which reaction would follow a given agent (see Hans Jacob). It is our opinion that post-vaccinial encephalitis may be similarly considered. De Vries goes more deeply into the histological picture and sees several other possibilities.

(A) *Toxic encephalopathy*

After every vaccination there is a viremia and often a septicemia. Thus, there is always a varied amount of intoxication of the entire body which can lead to malaise, reaching its peak at the 4th or 5th day post-vaccination. The malaise and fever may force the patient to cease work (Sissingh, see page 29). On rare occasions we may see a case in which these symptoms are very much intensified: headache, dullness and meningism may be accompanied by convulsions. If the patient succumbs and the cerebrum is examined, we see: (1) a slight meningeal exudate. If this is increased we speak of 'meningitis serosa'; (2) hyperemic meninges containing small amounts of lymphocytes and polymorphonuclear leucocytes, (3) lymphocytic infiltration of the parenchyma surrounding some of the vessels.

This more or less corresponds to the non-suppurative meningo-encephalitis of Van Bogaert. De Vries classifies the following case as belonging to this group.

Child P., was born blind. The mother had had German measles during the first trimester of pregnancy. (We were unable, even after lengthy questioning, to obtain full particulars concerning the mother's illness.) The primary vaccination took place at the age of 5½. Six days later, the child became listless and the temperature rose to 40° C, at which point she suffered

[text continued p. 38]

(B) The activation theory has always had its supporters, even to the present day In 1949, Pison pointed to the activation of a latent viru as a causative agent for post-vaccinial encephalitis. We are confronted therefore with a condition known as commensal infection (V... Loghem) In this regard we consider the lowered resistance of the patient as a primary factor and the activating etiological agent secondary factor.

We know from the literature and also from personal expe... that in the genesis of infectious diseases conditions that lower re... play a rôle (trauma, malnutrition, disturbances in the central regula... of various vital functions whether organic or functional) As a ... of this lowered resistance the infectious agent gets its chance It is in no way strange, therefore, that in the genesis of post-vaccinial encephalitis consideration should be given to the possibility that the vaccination itself is responsible for lowered resistance This would pave the way for a latent encephalitogenic virus This reasoning is supported by the fact that previously we never, or scarcely ever, encountered encephalitis after vaccination

After the first world war there were many cases of epidemic encephalitis This served as a possible solution to the problem since we then had a combination of the vaccine and an encephalitogenic virus (Stenvers). As an argument for this theory, use has been made of the sporadic quality of post-vaccinial encephalitis as regards time and place. This would fit in with the presence or absence at the time of vaccination of the agent causing encephalitis In this light the strange occurrence of three cases of post-vaccinial encephalitis after 36 vaccinations performed on the Island of Marken can be viewed in the light of this theory. It also might be used to explain the occurrence of several cases in one family.

Recently the local occurrence of cases of encephalitis was used as the starting point for a study. Special attention was paid to the possibility of the occurrence of ... ic virus in animals

In addition to this ... the local occurrence, we have to consider ... receive attention when we discuss 'en...

A point in favour of the ... occurrence at different ages. Th...

This demyelinization and microglial growth may also be sub-ependymal and sub-pial, the so-called 'edge gliosis' (Wohlwill, C. de Lange, De Vries) seen with a slight meningeal reaction (Fig 7)

In the spinal cord, increases of glia can be observed along the radiations of the posterior roots, the efferent veins, and the afferent arteries. The affected areas of the cerebrum as well as the cerebellum are generally localized in the white matter, hence the inclusion of the condition under the group 'leuco-encephalitis' (Pette) This localization in the white matter becomes less and less clear the more caudally one makes sections (Van Bouwdijk Bastiaanse, Turnbull and Mc-Intosh, Pette, Leiffer, Oesch, Finley and others). This means that in the brain stem (thalamic nuclei, globus pallidus, nucleus caudatus, substantia nigra) and in the spinal cord we shall find affected areas in the grey matter. Here, there is very often a neuronophagia (De Vries, Van Bouwdijk Bastiaanse, Querido, Wiersma) Suppan reported that the incidence of localizations in the mid-brain and surrounding the fourth ventricle is higher in children under the age of 5 than in adults Perdrau described early lymphocytic and plasma cell infiltration of the spinal ganglia. This changing of the histological picture at different levels is not an isolated phenomenon: in acute anterior poliomyelitis we often see that the bulbar reactions are more benign and transient (the localization is more dangerous!) than the spinal ones

The meningeal reaction shows itself as an infiltration of lymphocytes and large mononuclear cells; we never see plasma cells. The vascular reactions and haemorrhages are of an unknown nature (Lumsden, Van Gehuchten, Falcon) The parenchyma is normal around the infected areas, i.e. there is neither a diffuse oligoglial increase nor an infiltration about the small vessels

According to De Vries the histological picture in the affected areas is fully developed by the 11th day after vaccination, regardless of the duration of the clinical symptoms In cases of longer duration, the areas may become confluent through a more diffuse microglial perivascular infiltration, which means that the greatest degree of infiltration was not immediately around the vessel. In addition, we may see fat-granule cells in areas of greater necrosis.

We should now like to consider the problem already mentioned of the connection of the clinical picture with the anatomical background

called by De Vries: peri-venous demyelinating microglial encephalitis. In 1939, Comby pointed out the various reaction patterns of the nervous system following vaccination, and Hans Jacob, in 1948, emphasized them further. In 1950, in an article entitled "Post-infectious encephalo-myelitis and multiple sclerosis", Ludo van Bogaert described several possibilities of cerebral reaction following infectious diseases. In addition to the peri-venous encephalitis, he differentiated: (1) non-suppurative lymphocytic meningo-encephalitis, and (2) haemorrhagic pseudo-encephalitis.

Constitutional factors were considered to decide which reaction would follow a given agent (see Hans Jacob). It is our opinion that post-vaccinial encephalitis may be similarly considered. De Vries goes more deeply into the histological picture and sees several other possibilities.

(A) *Toxic encephalopathy*

After every vaccination there is a viremia and often a septicemia. Thus, there is always a varied amount of intoxication of the entire body which can lead to malaise, reaching its peak at the 4th or 5th day post-vaccination. The malaise and fever may force the patient to cease work (Sissingh, see page 29). On rare occasions we may see a case in which these symptoms are very much intensified: headache, dullness and meningism may be accompanied by convulsions. If the patient succumbs and the cerebrum is examined, we see: (1) a slight meningeal exudate. If this is increased we speak of 'meningitis serosa'; (2) hyperemic meninges containing small amounts of lymphocytes and polymorphonuclear leucocytes, (3) lymphocytic infiltration of the parenchyma surrounding some of the vessels.

This more or less corresponds to the non-suppurative meningo-encephalitis of Van Bogaert. De Vries classifies the following case as belonging to this group.

Child P., was born blind. The mother had had German measles during the first trimester of pregnancy. (We were unable, even after lengthy questioning, to obtain full particulars concerning the mother's illness.) The primary vaccination took place at the age of 5½. Six days later, the child became listless and the temperature rose to 40° C, at which point she suffered

(text continued p. 38)

This demyelinization and microglial growth may also be sub-ependymal and sub-pial, the so-called 'edge gliosis' (Wohlwill, C. de Lange, De Vries) seen with a slight meningeal reaction (Fig 7)

In the spinal cord, increases of glia can be observed along the radiations of the posterior roots, the efferent veins, and the afferent arteries The affected areas of the cerebrum as well as the cerebellum are generally localized in the white matter, hence the inclusion of the condition under the group 'leuco-encephalitis' (Pette) This localization in the white matter becomes less and less clear the more caudally one makes sections (Van Bouwdijk Bastiaanse, Turnbull and Mc-Intosh, Pette, Leiffer, Oesch, Finley and others). This means that in the brain stem (thalamic nuclei, globus pallidus, nucleus caudatus, substantia nigra) and in the spinal cord we shall find affected areas in the grey matter. Here, there is very often a neuronophagia (De Vries, Van Bouwdijk Bastiaanse, Querido, Wiersma) Suppan reported that the incidence of localizations in the mid-brain and surrounding the fourth ventricle is higher in children under the age of 5 than in adults Perdrau described early lymphocytic and plasma cell infiltration of the spinal ganglia. This changing of the histological picture at different levels is not an isolated phenomenon· in acute anterior poliomyelitis we often see that the bulbar reactions are more benign and transient (the localization is more dangerous!) than the spinal ones.

The meningeal reaction shows itself as an infiltration of lymphocytes and large mononuclear cells; we never see plasma cells The vascular reactions and haemorrhages are of an unknown nature (Lumsden, Van Gehuchten, Falcon). The parenchyma is normal around the infected areas, i e there is neither a diffuse oligoglial increase nor an infiltration about the small vessels

According to De Vries the histological picture in the affected areas is fully developed by the 11th day after vaccination, regardless of the duration of the clinical symptoms In cases of longer duration, the areas may become confluent through a more diffuse microglial perivascular infiltration, which means that the greatest degree of infiltration was not immediately around the vessel. In addition, we may see fat-granule cells in areas of greater necrosis

We should now like to consider the problem already mentioned of the connection of the clinical picture with the anatomical background

called by De Vries· peri-venous demyelinating microglial encephalitis. In 1939, Comby pointed out the various reaction patterns of the nervous system following vaccination, and Hans Jacob, in 1948, emphasized them further. In 1950, in an article entitled "Post-infectious encephalo-myelitis and multiple sclerosis", Ludo van Bogaert described several possibilities of cerebral reaction following infectious diseases. In addition to the peri-venous encephalitis, he differentiated. (1) non-suppurative lymphocytic meningo-encephalitis, and (2) haemorrhagic pseudo-encephalitis.

Constitutional factors were considered to decide which reaction would follow a given agent (see Hans Jacob) It is our opinion that post-vaccinial encephalitis may be similarly considered De Vries goes more deeply into the histological picture and sees several other possibilities.

(A) *Toxic encephalopathy*

After every vaccination there is a viremia and often a septicemia Thus, there is always a varied amount of intoxication of the entire body which can lead to malaise, reaching its peak at the 4th or 5th day post-vaccination. The malaise and fever may force the patient to cease work (Sissingh, see page 29) On rare occasions we may see a case in which these symptoms are very much intensified headache, dullness and meningism may be accompanied by convulsions. If the patient succumbs and the cerebrum is examined, we see (1) a slight meningeal exudate. If this is increased we speak of 'meningitis serosa', (2) hyperemic meninges containing small amounts of lymphocytes and polymorphonuclear leucocytes, (3) lymphocytic infiltration of the parenchyma surrounding some of the vessels.

This more or less corresponds to the non-suppurative meningo-encephalitis of Van Bogaert De Vries classifies the following case as belonging to this group

Child P, was born blind The mother had had German measles during the first trimester of pregnancy (We were unable, even after lengthy questioning, to obtain full particulars concerning the mother's illness) The primary vaccination took place at the age of 5½ Six days later, the child became listless and the temperature rose to 40° C, at which point she suffered

text continued p 38!

a convulsion She remained comatous and died after 10 hours Cerebrospinal fluid: cells 7/3, total protein 14 mg%.

Cornelia de Lange examined the brain and diagnosed the case as a fulminating post-vaccinial encephalitis. De Vries later examined the same cerebrum and reported the following. The brain, as well as the internal organs, is very hyperemic, the pia capillaries are especially so. There is no clear swelling of the cerebrum. The sections show, in addition to a slight meningeal infiltration, a diffuse slight glial increase which is not peri-venous. Most of the round nuclei of the oligoglia lie in rows along the vessels, mostly capillaries or pre-capillaries. Many of these glial cells contain protoplasm which can be coloured with Nissl's stain but which does not form a syncytium with that of other cells as is the case with collections of microglia cells. No changes are *observable in the myelin sheaths. As a curiosity, we may also* mention the calcium-like concrements present in the walls of the vessels in the caudate nucleus and heterotopic grey matter in the occipital ventricular wall (a remainder of the intra-uterine rubella?)

Fig 8 is reproduction of the genealogical tree of the patient's family. To sum up the findings.

(1) The child had obviously degenerative stigmata (among others, the cerebral heterotopia).

(2) It is very probable that the mother had rubella during her pregnancy.

(3) There are vascular conditions in the family which give rise to symptoms at an early age (calcium in the vessel walls!).

(4) We see degenerative stigmata in the family.

(5) The child died of a cerebral disorder following a vaccination.

It is very possible that it was because of this predisposed cerebrum that the reaction was so explosive We wonder whether the vascular anomalies may not themselves have been responsible for the type of the histo-pathological picture, altering it so that it no longer fits into our scheme As we have already mentioned, the non-suppurative meningo-encephalitis of Van Bogaert belongs to this group.

(B) Sometimes the vaccinia is followed by an actual *encephalitis,*

which is clinically a post-vaccinial encephalitis, but which may show different pathological-anatomical pictures De Vries does not consider *it justified to regard this as a cerebral aggravation or condensation* of the vaccinia septicaemia. He considers it very probable that there is a toxin-antitoxin reaction present.

(C) *Acute haemorrhagic encephalopathy* (probably corresponding to the 'haemorrhagic pseudo-encephalitis' of Van Bogaert) De Vries describes the following case.

Patient de G, aged *13* Successful primary vaccination at the age of 1½. Epileptic fits since her third year. At the age of 13 she was an imbecile epileptic. Six days after revaccination (without any visible results) she became sick, listless and showed muscular spasms. The next day she had an epileptic fit followed by a progressive coma Bronchitis developed and she died on the ninth day after the revaccination The brain showed much oedema and hyperemia, many areas of subcortical demyelinization and glial increases with central or ring-shaped haemorrhages The demyelinized areas were round and transversed by many myelinated strands. The masses of microglial cells were found only in the softened, necrotic centres

This case was considered by Van Bouwdijk Bastiaanse and Querido as a typical post-vaccinial encephalitis but De Vries wonders whether this may not be Hurst's acute haemorrhagic leuco-encephalitis, which he (Hurst) considered one of the typical cerebral allergic reactions We also see such a picture in experimental encephalitis (Wolf, see page 58).

(D) *Complications after revaccination*

Van Bouwdijk Bastiaanse stated that the encephalitis seen following revaccination (with a resulting reaction of immunity) differs from the typical microglia encephalitis. We do, however, see this typical picture when the revaccination shows a primary reaction In cases of post-revaccinial encephalo-myelitis we see round areas of demyelinization which look like oil stains There are little or no peri-vascular microglia masses, but there is pseudo-neuronophagia and degeneration of nerve cells The histological pictures seen following revaccination vary so widely that De Vries does not consider it possible to classify

these rare cases of post-revaccinial encephalitis until we have gained more experience.

(E) *Pyemic-septicaemic encephalitis*

Here we are probably dealing with a cerebral inflammation caused by secondary infection. We see small multiple areas, sometimes with a central group of bacteria Here and there are small areas crowded with polymorphonuclear leucocytes: the precursors of abscesses. Not infrequently, all we see are small necrotic spots with collections of glial cells The patient described by De Vries was a diabetic. He became ill on the sixth day post-vaccination and died on the ninth day. This condition probably developed from the viremic-septicaemic stage and had a shorter incubation period than is generally seen in post-vaccinial encephalitis.

(F) *Acute anterior poliomyelitis* has been reported several times in connection with vaccination (Heidema, Burgerhout, Verjaal).

(G) *Panencephalitis* has also (although rarely) been seen. This has been verified by patho-histological investigation.

(H) *Epidemic encephalitis* was seen once by De Vries in an infant.

On surveying the pathological anatomy, the value of the 'classical' perivenous demyelinizing microglia encephalitis becomes somewhat less than absolute Cornelia de Lange drew attention to this problem when she wrote in *1948*. "neben Hyperaemie kann mann auch Oedem finden, Nekrosen, Blutungen, beginnende Thrombosen und Ausschwitzung von Plasma aus den Gefässen". De Vries also speaks of our sometimes finding things whose significance is not clear to us The degree of perivascular lymphocytic infiltration varies greatly De Vries describes the case of a young man of 19, who succumbed *14 days after a vaccination, he found a degeneration of the substantia nigra*, showing many swollen (sometimes pigment-free) cells or cell-shadows without any infiltration This picture was quite different from what we generally expect in a microglia encephalitis The diagnosis of acute anterior poliomyelitis could not be considered because in

that condition we always see the progression: cellular disease, neuronophagia, and inflammation. We must mention, however, that this cerebrum showed several old scars.

In a child of 3½ years De Vries found many oligoglia nuclei in the peri-vascular area. During the period of vaccination this child had been treated with serum for pertussis.

On reviewing all of the above, we can say that if the earlier reports (Van Bouwdijk Bastiaanse, Bouman and Bok, Van Hasselt, Bijl, Terburgh, Turnbull and McIntosh) on the pathological anatomy of post-vaccinial encephalitis were monotonous, this is certainly no longer the case! This divergence from the 'classical' picture, however, does not seem so serious when we consider that all the unusual variations described by De Vries were found in cases whose histories revealed, in addition to vaccination, other occurrences which may very well have modified the histological picture. The future will have to prove the accuracy of this hypothesis.

It remains difficult to draw any far-reaching conclusions from the pathological-anatomical picture, partly because the central nervous system is very limited in its means of reaction (Spielmeyer, De Lange, *Report of the Encephalitis Commission, 1932*).

We should now like to turn our attention to the question of whether or not post-vaccinial encephalitis is ever seen in young children. In 1938, Julius attempted to show by statistical means that encephalitis following the vaccination of young children must be considered as a coincidental occurrence. He found the same incidence of encephalitis in vaccinated and non-vaccinated children of this age. Peeters and Neurdenburg protested strongly against this point of view: they considered nothing proved one way or another concerning either the coincidental or the causal theories of 'post-vaccinial' encephalitis in young children. Some time ago, under the auspices of the T.N.O., a statistical analysis was carried out which showed that the coincidence found by Julius was impossible. De Vries examined the cerebra of 20 children under the age of 1½ who died shortly after vaccination, and found:

5 clear-cut cases of other diseases (embolus, meningococci, polio-myelitis, sinus thrombosis, epidemic encephalitis,

3 cases of toxic conditions (eczema vaccinatoria, enteritis, pneumonia) in addition to vaccinia;

4 cases of cerebral oedema;

11 cases of a toxic picture, of which 5 had shown convulsions; and 1 case in which the cause of death was probably not cerebral.

Why was he unable to find the picture of a microglia encephalitis in children under the age of 1½? Not because of an absence of myelin, for there was sufficient myelin present. According to Flechsig, the association centra are myelinated after birth, at which time the projection centra are already myelinated. At birth, myelination of the brain stem, medulla oblongata and spinal cord has already begun *and is practically complete by the age of 1½. Let us follow De Vries's* arguments still further. Microglia is also present at the age of 1½; according to Hortega these cells penetrate the nervous tissue from the meninges during the prenatal period and have completed their migration after a period ranging from several days to several weeks. Evidence for this is the microglial collection seen in infants suffering from other diseases (*e.g.* poliomyelitis) The absence of the microglial character in the encephalitis seen in (other) exanthematous diseases is also a problem: Dagnélie and Dubois described four cases of measles encephalitis and (like Musser and Hauser) found no microglia encephalitis. They also reported a case of encephalitis following varicella: some degree of demyelinization, but no microglia encephalitis. Zimmermann and Yanet described the case of a baby girl of 13 months who died 4 days after a varicella eruption; they found some demyelinization but no increase of microglia. Dubois, Ley and Dagnélie mention seven cases of encephalitis following pertussis, none of which showed the picture of a microglia encephalitis.

A great difficulty in the assessment of the value of the presence or absence of demyelinization is that we know nothing concerning the nature of the process itself. We see it in so many varied conditions. fat embolia, pinpoint haemorrhages, bacterial emboli (Wolf) Here we are tempted to regard the vascular occlusion or changes as the cause, but why are the axons undamaged? They are known to be very sensitive to an oxygen deficiency. Krogh and Eppinger consider it possible that the demyelinization is brought about by some substance formed in the tissue itself. This would then secondarily

cause the demyelinization. We can then hypothesize that the abnormal metabolism caused by vascular occlusion forms a substance having a demyelinating effect. In support of this theory is the fact that demyelinization is absent in the very early stages (Graffar) We can extend the theory still further: the toxic agent enters the arterial blood stream and reaches the parenchyma, where it causes tissue damage, with or without a reaction, leading to the liberation of a demyelinating substance ((phosphatase?) Verlinde, Kret and De Vries) This substance is spread diffusely throughout the parenchyma and is not sufficiently concentrated to do serious damage. It then flows towards the venous system, with the result that the concentration is increased and concomitantly the toxic (i e. demyelinating) effect also. This may also serve to explain why the demyelinization is perivenous. If we assume that the substance passes through the venous wall, we arrive at a retrograde spread in regard to the normal flow.

There is little support for Jacob's theory that the demyelinization is caused by a diffusion of plasma (a hyperergic inflammation).

After this discussion of the nature of demyelinization we proceed further with our problem. The other types of viral encephalitis (poliomyelitis, epidemic encephalitis, herpes encephalitis) seen in children of one year or younger show the same histopathological picture as in the adult cases De Vries can give no explanation for the fact that these viral encephalitides show the same picture in adults and infants, whereas in the case of the para-infectious and post-vaccinial encephalitis the divergence is so great In 1949, Brante summed up the various changes which the composition of myelin undergoes during life Edgar found significant differences between the chemical composition of myelin in young and adult rabbits. It is very possible that there is a connection between this difference in chemical composition and the means whereby the myelin reacts In trying to compare encephalitis of various etiologies, we must never forget the warning by Rivers, "no known virus acting directly on the central nervous system produces a perivascular demyelinating type of encephalitis", which may mean that here we are confronted with an entirely different sort of process

We should now like to consider whether or not we may classify the

changes seen in children as belonging to the fulminating microglia encephalitis. Unfortunately, it is not possible to compare the rapidly fatal cases in infants with those having had a longer course because the latter are not available. Thus, we have to compare fulminating and slower adult cases. First of all, we should like to go back to the case of child P, described on page 35. De Vries wonders whether this case might not be more suitably considered as a toxic vaccinia' in encephalitis we should expect a much longer incubation period Doring describes two cases, one of which, a man of 27, had an incubation period of 13 days In such cases we generally find a typical microglia encephalitis, but here this was not found. De Vries mentions the possibility of this being a case of slowly-developing microglia encephalitis in which death was caused by a rapid formation of cerebral oedema. This would also serve to explain the acute clinical course.

Pette (1947) divides the course of the microglia encephalitis into two stages. Firstly, vascular dilatation with slight infiltrations and perivascular glia (oligoglia?). Secondly, the appearance of demyelinization with pronounced collections of micro- and oligo-glia and of fat-granule cells surrounding the vessels Is it possible when we are unable to find the picture of a microglia encephalitis at post-mortem examination that convulsions have caused an early death? Cornelia de Lange rightly warns of the danger of postulating organic cerebral damage when dealing with convulsions in children.

It would scarcely appear justified to say (as does Gorter) that no encephalitis following the vaccination of young children is a real post-vaccinial encephalitis (see Julius). Gorter believes that the appearance of convulsions in a child depends more on the constitution of the child than on the acquired illness. This may be true in some cases but it is definitely not valid as a generalization. The possibility is not excluded that the same constitutional factor may cause a predisposition not only to the reaction with convulsions but also to the cerebral reaction in the organic sense This, however, does not bring us any closer to a solution of the problem We do not believe that we can say any more than that the possibility exists that convulsions occur without any cerebral damage even though the two generally go hand in hand.

De Vries describes two cases in which after an illness of one day, the patients died 11 and 13 days after vaccination Histologically, there was a clear microglia encephalitis.

Since the cases described as fulminating show oligoglia reactions and areas of infiltration around the cortical vessels (arterioles as well as veins), De Vries finds it difficult to consider these as early stages of microglia encephalitis. He has seen the 'toxic encephalopathy' eleven times in children of one year and younger, but has never seen a more advanced stage. Thus, he lacks the trait d'union with the microglia encephalitis. He suggests, therefore, that as long as we are unable to *prove that the vaccinia virus is the cause of the encephalitis, we should* consider the 'toxic encephalopathy' as being connected with the vaccinia rather than the post-vaccinial encephalitis. From our point of view, it has hitherto not been disproved that reactions in children are different from those in adults. We do see different pictures but may these not be caused by other properties of the 'terrain'? (Comby) We see a parallel when we consider skin reactions: how often do we not see eczema infantum disappear as the child becomes older? The *manner of reacting changes with age And who is surprised when this* child, now older, suddenly begins to have attacks of asthma? Another example of differences in reaction is seen in the vaccination itself: very young infants do not react to vaccination by developing a good immunity. It is also known that young animals do not readily produce antibodies: Doorschodt showed that the titer of anti-vaccinia-haemaglutination (an index of the immunity) is proportional to the age.

The above are all separate items which (at present) we are unable to integrate.

ETIOLOGY

We have seen in the preceding chapters that the post-vaccinial encephalitis is a clear-cut entity in which we can expect various histological pictures (after the elimination of coincidental diseases of the central nervous system occurring after vaccination) The arguments for uniform histological changes described by earlier investigators have been considerably weakened.

We now have to consider the factors that play a role in post-vaccinial encephalitis. We shall see at the end of the discussion that a definite solution has not been found.

If we return once more to the *Report of the Encephalitis Commission, 1932*, page 195, we read: "The chapter concerning etiology is a painful chapter After working on the problem for five years, the commission is as far from the solution as it was in 1925, when the question first arose" Now, many years later, we read this passage again and realize that we have little to add

We have learnt through the almost constant length of the incubation period that there is a connection between vaccination and the following encephalitis. Most probably, the incubation period for small children is different from that for adults (De Vries has recently pointed this out) and the pathological-anatomical changes in children are of another type than are seen in the majority of adults. We cannot agree with those investigators who consider encephalitis after vaccination of very young children coincidental (Julius, Peeters and Neurdenburg)

If there is a relationship between the introduction of the vaccine into the body and inception of post-vaccinial encephalitis, what are the possibilities?

(A) The theory of superinfection Under this theory we accept the fact that the cowpox material is the carrier of

(1) Bacterial contamination. This would serve as the causative agent for the encephalitis

(2) Non-bacterial contamination due to a concealed virus in the cowpox material which causes the post-vaccinial encephalitis.

(3) Toxins

(B) The cowpox material activates a circulating virus. It could do this by making the virus pathogenic or by lowering the resistance of the patient, thereby giving the virus its chance. This is the commensal theory.

(C) The cowpox material causes the encephalitis

(1) The virus itself is 'encephalitogenic'.

(2) The virus gives off, via a certain change, an intermediate substance that has an encephalitogenic action

(3) The encephalitis is an allergic reaction to the presence of the virus

(A, 1) The possibility of bacterial infection caused by the vaccination was described in 1927 by Aldershoff. He, as well as Pette, was able to cause septicaemia in rabbits by vaccinating them with cowpox material containing the otherwise innocuous *Bacterium bipolaris*

Pondman came to the conclusion that vaccinated rabbits died after the vaccination because of pasteurellosis The assumption that *Pasteurella* had anything to do with post-vaccinial encephalitis was not substantiated Control vaccinations with neurolapine, in which sterility may be assumed, were also followed by clear-cut cases of post-vaccinial encephalitis Convincing evidence has never been found for bacterial contamination as a cause of post-vaccinial encephalitis

(A, 2) The possibility that a virus is brought in with the vaccine and is the cause of the encephalitis, has never been proved It was Bijl who worked on this theory His work, especially in regard to the herpes virus as a cause, never produced any conclusive findings.

Levaditi, among others, suggested the possibility of contamination of the vaccine with herpes virus He received the support of Gildemeister, Herzberg and Heuer, who demonstrated immunological relationship between the herpes and vaccine virus Positive findings in support of the herpes contamination theory have never been found, Gorter, Blum and Boutier pointed out that previously encephalitis following vaccination never appeared At that time the vaccine did

circulating encephalitogenic virus. More convincing is the fact that post-vaccinial encephalitis also occurs when different cowpox material is used.

Experiments with animals have not yielded satisfactory results. It has not been possible to culture an encephalitogenic virus from organs of patients who died of post-vaccinial encephalitis.

Using cerebral tissue of the same patients, it was only occasionally possible to culture the cowpox virus. Verlinde, however, by vaccinating a cynomolgus ape with a combination of cowpox virus and Columbia S K. virus, succeeded in producing an encephalitis which in part showed the histo-pathological picture similar to that of a microglia encephalitis with demyelinization.

In his dissertation, Hoelen discussed success in culturing a virus from the naso-pharynx of patients with post-vaccinial encephalitis that was similar to the herpes and encephalitis lethargica virus.

Upon reviewing the above we can say: there are many arguments in favour of the activation theory but no conclusive proof. There are many infectious diseases to which the above remarks could apply and yet we cannot consider that activation plays a rôle in them.

As an example let us consider acute anterior poliomyelitis. We know that during epidemics many people come in intimate contact with the poliomyelitis virus (Biemond). Yet so few show clinical symptoms! Nevertheless, very few clinicians doubt the etiology of the disease, regardless of its elective nature.

The mechanism of activation can sometimes play a rôle and this we accept (See the chapter on pathological anatomy in which we described changes after vaccination that were different from the usual picture. Here we could have activation and lowering resistance playing a rôle)

Uiberall believes he has disproved any relationship with the poliomyelitis virus During an epidemic of poliomyelitis a very large group was vaccinated and not a single case of post-vaccinial encephalitis was observed Puntigam and Berger investigated all cases of poliomyelitis in Vienna from 1951 until 1956 to find out if there was any difference in occurrence of paralytic forms of poliomyelitis between two groups The first group was vaccinated against smallpox, the

second was not. They could not find any influence of vaccination in this respect

The virus of lethargic encephalitis gives a different histo-pathological picture, which makes it very improbable that there is any connection between it and post-vaccinial encephalitis.

From the point of view of epidemiology even less relationship can be found between post-vaccinial and lethargic encephalitis. (France had many cases of encephalitis lethargica without any increase in the number of cases of post-vaccinial encephalitis) De Vries once encountered a case of encephalitis lethargica after vaccination Since this is so rare we cannot consider it the rule.

The description given above concerning the pathology of lethargic encephalitis also holds true for acute anterior poliomyelitis. The latter particularly affects the ganglion cells, whereas in post-vaccinial encephalitis the ganglion cells are often the only normal patches in an area of destruction Epidemiologically there is no relationship between the two (see above, Uiberall)

In experimental work with animals we do not meet with any convincing arguments for the connection between the virus of poliomyelitis and post-vaccinial encephalitis

In conclusion we should like to say that up to the present time it has not been possible to show a relationship between any virus, other than the vaccinia virus, and post-vaccinial encephalitis This is true for the so-called neurotropic viruses as well as for unknown encephalitogenic viruses.

This does not mean that no work is being done in this field Nanning, in particular, is working on the problem. He sees a possible connection between the occurrence of post-vaccinial encephalitis and the presence of the encephalitogenic virus in domestic animals. His finding of the Columbia S K virus in the faeces of a patient, although demonstrated only once, was the foundation for Verlinde's experiments

(C) The cowpox virus as etiologic agent

The argument that before 1924 no cases, or only sporadic cases, of post-vaccinial encephalitis were seen has been used to refute the above-mentioned hypothesis One does see in the literature, however, descriptions of complications after vaccination which suggest the

posibility of post-vaccinial encephalitis but this is by no means conclusive (Kaiser, 1801; de Caro, 1801; *Freud, 1897; Comby, 1907;* Turnbull, 1912).

The following extract from the *Report of the Encephalitis Commission, 1932*, can serve as our point of reference: When a patient in the course of typhoid fever develops osteomyelitis, or at the end of lobar pneumonia a meningitis, no one would consider the activation of an unknown virus as the most plausible explanation. The same report continues: *One would think in the first case of typhoid bacilli* and in the second case of pneumococci. If no typhoid bacilli and *no pneumococci were found and if no other pathological micro-*organism were found, one would still not assume that an unknown virus was activated. One would, however, ask: Why were no typhus bacilli or pneumococci found? So much for the report.

Why special complications occur in these cases still remains a mystery. This same applies to post-vaccinial encephalitis The difficulty in finding a solution is for a great part due to the caution which is needed in *considering etiological possibilities.*

Every *neurologist knows of a case in which the parents tell of their child falling and thereafter showing signs of cerebral concussion.* After the accident the child is never the same again. Walking is unsure and there are complaints of headache, with or without vomiting. On examination we find an ataxia, and eye examination shows choked discs. We find other symptoms indicating *increased* intracranial pressure.

The accepted story of events of trauma capitis – intracranial haematoma – *neurological picture is often a misunderstanding* The cause of the fall appears, on further questioning, to be insufficient. The child has recently been a little unsure in walking and as result had fallen. A tumour in the posterior cranial fossa serves to explain the entire sequence of events.

This example shows us how cautious we must be in drawing conclusions on the basis of signs and symptoms seen in particular sequence. In the above example a solution was *found How different in the case* of post-vaccinial encephalitis! If we do not accept the virus itself as being the causative agent have we another explanation? We have tried to show in the above that support in other directions is lacking.

Is it possible to demonstrate the vaccinia virus in post-vaccinial encephalitis?

After vaccination the pox pustule makes its appearance, it reaches its maximum between the eighth and twelfth day. This is about the same as the incubation period for the encephalitis and vaccinia generalisata After the fifth day antibodies are produced After the eighth day it is possible to demonstrate the specific precipitation reaction (Knox, Finley)

In an 'accelerated local reaction' we have seen an 'accelerated cerebral reaction' (Comby, Querido) According to Eckstein the virus circulates in the blood from the third to the tenth day.

From this we can consider the possibility of the vaccinia virus causing a cerebral reaction during the period of viraemia. This possibility is very slight since we have seen that it has never been possible to cause a picture of post-vaccinial encephalitis after the injection of the virus. It is true that after introducing a large quantity of the virus directly into animal cerebri encephalitis can be seen Here, *however, the technique used is so far from the natural course of* infection in post-vaccinial encephalitis that little information can be hoped for by further experimentation in this direction.

Rivers has pointed out that no known virus that works directly upon the cerebral tissue can produce a microglia encephalitis. Occasionally, it has been possible to demonstrate the virus in the cerebrospinal fluid and the brain tissue of patients who died of post-vaccinial encephalitis

The fact that this is not always possible is an argument against the virus as the encephalitogenic factor. An argument for the virus as causative agent is the fact that it has only once been possible to demonstrate a virus other than the vaccinia virus (Echo-virus by Verlinde) Positive findings on patients who died after vaccination due to other causes have never been described

The frequent occurrence of negative findings led to a belief that there might be a connection with what Levaditi called the 'neuro-infections mortelles autostérilisables' in which, in the course of the infectious process, all viruses are destroyed. This is supported by the fact that the cerebral tissue of patients who died of post-vaccinial encephalitis was able to inactivate the vaccinia virus

Another possibility is that the virus is destroyed in the cerebral tissue and that the products of this destruction, being carried on *towards the venous system, give the picture of a microglia encephalitis* (see page 43). Whether liberated phosphatase (Verlinde, Kret, De Vries) or some other demyelinating material (Wolf) plays a rôle here has yet to be proved. This might act as a starting-point for an explanation of the appearance of identical cerebral lesions in the various exanthematous diseases: we could postulate a substance 'X' which is liberated in the destruction of various viruses and which is responsible for the histological picture. Whether, in addition to 'X', other substances are liberated which, in the case of different viruses, are not identical has nothing to do with the matter under consideration. There are many attractive aspects to this line of reasoning, but more facts will have to become known before it gains support. Since none of the above theories are conclusive, other explanations were sought. A good one was thought to have been found in the conception: allergy. This was first pointed out in 1927 by Glanzmann and later by Van Bogaert. The 'allergic reaction of the central nervous system' is, however, a difficult concept to understand and much has still to be learned about it. We are thinking in particular about the pictures called allergic reaction, in which demyelinization is the foremost phenomenon. However, there are other pictures described: Van der Horst describes the symptomatic psychosis and allergic reaction following pertussis vaccination; Hurst, what he calls the acute haemorrhagic leuco-encephalitis; and Jacob, many types of possible allergic cerebral reactions.

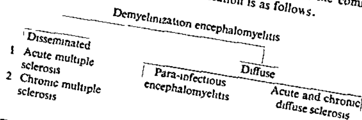
An allergic reaction takes place by the sudden reaction between antigen and antibody, whereby the intensity of the reaction need not parallel that of the immunity reaction Finley defines the latter as a specific biochemical reaction, brought about in the body by a foreign body, which gives rise to a specific immunity or hypersensitivity of the body for that agent. Apart from this vague description, he says nothing concerning what may take place in the cerebrum. Hansen, in his book on allergy, characterizes the allergic reaction by three points:

(1) Sudden, paroxysmal beginning
(2) Relatively transitory character

(3) Usually rapid and complete regression.

The basis for the above are smooth muscle spasms, vascular spasm, serous exudation and especially eosinophile infiltration The latter is seen where there is an intensive antigen contact with a sensitized tissue In cerebral reactions we are generally confronted with haematogenous spread, which raises problems which do not occur where the antigen comes into direct contact with the reacting organ Hansen wonders whether other factors (trauma, infections) may not have formed a locus minoris resistentiae (see page 61). Here again we see no sharp definition of 'cerebral allergy'. Peers, in his description of allergic encephalomyelitis, mentions only the means by which this picture is produced, considering it *a priori* allergic. He does not elaborate on the essence of the production of this picture, but says 'allergic encephalitis is an inflammatory and degenerative disorder of the central nervous system of certain susceptible animals, which is produced by the parenteral injections of sterile emulsion of brain tissue'. This sounds rather decisive but actually does not help us much

Pette classifies all the diseases in which demyelinization is seen under one heading He considers the demyelinization the common and most important sign His classification is as follows.



To what extent this grouping together of these diseases on the basis of a pathological-anatomical symptom is valid remains to be seen We see demyelinization in so many different, and probably unconnected, conditions Some believe that the areas of demyelinization are brought about via the vascular system The walls of the vessels (especially the veins) are supposed to assume a looser structure during this initial stage, and plasma exudes through the wall, which is then

more or less infiltrated by lymphocytes and plasma cells At the same time we see inflammatory and reparatory growth of the glia. The vascular dilatation is believed to indicate an early involvement of the vasomotor apparatus, which may actually be the initial stage of the entire process. After the above stages, we see the appearance of demyelinization, which may or may not be accompanied by damage to the axons and pronounced growth of microglia, oligoglia and fat-granule cells surrounding the vessels (see below). In some of the acute cases death occurs so early that we see no demyelinization. (De Vries believes that these cases represent an entirely different condition. He has seen this picture often in young children, but has never seen demyelinization.) Pette considers several factors important in deciding whether or not this picture will develop: in some demyelinating disorders the endogenic factors are most important, while in others (e.g. para-infectious encephalitides) it is the exogenic factors which are outstanding Other factors such as climate, trauma, etc., also play a rôle. Pette also attempts to describe a common mechanism for the development of the demyelinization encephalomyelitides. In order for a reaction to take place, not only is the stimulus important, but also the 'Reaktionsbereitschaft' of the organism or tissue, which ebbs once the reaction has begun, only to flame up again in response to a new and perhaps non-specific stimulus. The reaction is hyper-, hypo- or an-ergic, depending on the constitution The stronger the antigen-antibody reaction and the 'Reaktionsbereitschaft', the more intensive will be the morphological answer (the allergic reaction). The 'Reaktionsbereitschaft' depends on hereditary factors, age, hormonal balance, etc., and these also determine the tissue specificity. To what extent an antigen determines the localization and type of the disorder is not known, but we do know that different allergens can give identical reactions and that the same allergen may give rise to varying reactions Klinge has pointed out that the conception of allergy means a breaking away from the old ideas concerning causation and illness, which, as the response of a living organism to a noxious agent, constitutes the essence of the pathology

Pette divides the demyelinization encephalo-myelitides, which he considers to be hyperergic reactions, into four stages

(1) Vascular dilatation causing slowing or stasis of the circulation.

This is accompanied by a looser structure of the vascular endothelium and a change in capillary permeability.

(2) Plasma exudation.

(3) Damage of the surrounding parenchyma (necrosis, haemorrhage, infiltration)

(4) Organization of the products of destruction and reaction: walling-off.

He points out that the changes develop from the vascular system and are of an explosive nature. He regards the reaction of the connective tissue as secondary Here the reaction of the glia is more evident than that of the mesodermal elements. If the patients do not die, demyelinization develops and, in very serious cases, axon-destruction

The picture described above does not appear to us to be completely applicable to post-vaccinial encephalitis The changes in capillary permeability would lead us to expect reactions in the areas around the capillaries, this we do not see.

Necrosis and haemorrhage are also rare findings Very striking is the finding of intact ganglion cells in the middle of damaged areas; this is difficult to explain on the basis of the above theory.

Whether it is permissible to group together all the demyelinating disorders in order to arrive at an explanation of the etiology remains, as we have previously mentioned, debatable We do find in the literature, however, descriptions of cases of post-vaccinial encephalitis in which remissions and exacerbations were seen (Hausmann, Stromgren), but does this justify classification with multiple sclerosis? This problem has recently been studied by Greenfield In considering the disorders which are grouped under the heading diffuse sclerosis, he differentiates three forms of demyelinization

(1) The 'inflammatory' type, familial and non-familial

(2) The 'metachromatic degenerative' type, familial and non-familial

(3) With 'epitheloid' or globoid" cells, familial.

Here again we see the division into obviously different pictures despite the common symptom of demyelinization (see De Vries)

It is simpler from the point of view of clinical course and pathological-anatomical changes to group the para-infectious and post-vaccinial encephalitides together

We have seen that there is still much uncertainty concerning the question of allergy and that a convincing explanation of cerebral allergy reaction has still not been arrived at. This is not to deny that many colleagues, especially those in the experimental field, have attempted to reproduce a demyelinization encephalomyelitis by means of 'allergy'.

In 1904, Heller and Bertarelli discovered that repeated injection of a filtered brain extract caused loss of weight and sometimes paralysis and death in guinea-pigs Unfortunately, the pathological-anatomical changes were not investigated.

In 1925, Koritschoner and Schweinburg repeated these experiments, using rabbits, and on examining the tissues microscopically found congestion, oedema and nerve-cell degeneration, but no demyelinization. The above was completely restricted to the spinal cord. There was no cerebral damage.

Riven, Sprunt and Berry, in 1933, repeatedly injected rabbits with watery cerebral emulsions or alcohol-ether extracts and produced what they called 'an allergic encephalitis'. The experiments of Lewis and Loomis (1924) revealed that the antibody production of guinea-pigs with active tuberculosis was greater than that of healthy animals. In 1929, this was supported by experiments with protein and horse serum (Diem and Schoenheit), they found that they could artificially raise the antibody production by the injection of dead tuberculosis *bacilli*.

In 1942, Freund published his findings on the powerful effect of the injection of tuberculosis bacilli combined with sterile lanolin and liquid paraffin.

Kopeloff and Kopeloff were the first to use the so-called Freund's adjuvans with cerebral extracts in experiments on apes and rabbits. In the latter animals they saw the production of paralysis, but unfortunately did not investigate the anatomical changes.

More recently, there has been an increase in the number of publications concerning the so-called allergic encephalitis (Kabat, Wolf, Bezer, Olitsky, Cazullo, Ferraro, and many others). In all these experiments the encephalitis is seen most clearly in the ape.

We see the following picture

(1) Foci around the veins and venules.

(2) These are clearest in the white matter, but also demonstrable in the grey matter of the brain-stem and the basal ganglia, less so in the cortex cerebri

(3) The larger veins are dilated (through paralysis of the wall or congestion?)

(4) Thrombosis is rarely seen.

(5) The endothelium is sometimes swollen

(6) The perivascular spaces are wide and contain monocytes and, less frequently, polymorphonuclear leucocytes and a few eosinophyl cells The number of cells increases later, at which time we see more lymphocytes and monocytes.

(7) In some areas we see narrow vessels (through pressure?).

(8) There are foci of demyelinization.

(9) Gliosis is seen in some areas

(10) Meningeal reactions are seen

Although there are points of agreement with post-vaccinial encephalitis, on closer examination there are obvious differences (see Chapter 5)

The supporters of this comparison may put forward as an argument the possibility of a rôle being played by the previous cerebral traumatism in post-vaccinial encephalitis This might, by destruction of cerebral tissue, sensitize the cerebrum. This was hinted at in 1923, by Levaditi and Nicolau Other authors too (De Vries, Van Bogaert, Bickers, Peust) consider previous cerebral traumatism as a possible important etiological factor.

It is not yet certain which substances are involved in the production of these experimental encephalitides Most investigators believe the white matter to be the most active, but Lumsden points out that in the cavia, human grey matter is the most active. An attempt has been made using fractionation, to isolate the active principle Halpern and others consider it to be myelin, but which constituent of the latter is most active is still not known

Morrison and others have experimented with lecithinase (prepared from *Clostridium welchii*), which produces hydrolysis of lecithin No conclusions could be drawn from this concerning the mechanism of demyelinization Verlinde and others were able to produce demyelinization by means of phosphatase, but the areas were not perivascular No demyelinization was caused by the intravenous injection of

phosphatase in apes. Phosphatase was, however, found to be present in the vaccinia virus and in staphylococci. Olitsky and Tal showed that the substance which produced a disseminated encephalomyelitis in mice may have been a lipoprotein (protolipid A and B).

Colover administered dead tuberculosis bacilli in addition to fractionated cerebral extracts. With some of the fractions he was able to produce an 'allergic' encephalo-myelitis. His opinion is that a non-lipoid fraction of the tuberculosis bacillus and a proteolipid of the cerebral substance (probably a haptene) together form the antigen.

In 1954, Wolf surveyed the many materials which were able to produce demyelinization. He placed great emphasis on the difficulties of judging the results produced by these substances.

We have as yet no answer to this difficult but interesting problem. The question arises whether we must accept a relationship between 'allergic' and post-vaccinial encephalitis despite the differences in pathological anatomy and means of provocation. Ferraro and others believe that it is not necessary to deny a relationship on the grounds of the differences, as long as we are aware of being on dangerous ground. It seems advisable to us to delay making a definite statement until more is known concerning the allergic reactions of the central nervous system.

We should now like to move on to the question of whether factors other than those already mentioned play a rôle in the production of post-vaccinial encephalitis. First of all, is the type of vaccine a factor? There has been no satisfactory proof of this. Perhaps a more complete investigation might prove profitable, but this is made difficult by the very sporadic appearance of the encephalitis. An attempt has been made to restrict the number of cases by importing vaccine from countries not having complications after vaccinations, but this has proved to be of no help.

In the Netherlands we have seen cases of encephalitis following the use of this so-called non-encephalitogenic virus (Van Bouwdijk Bastiaanse, Heinsius van den Berg and others). During the vaccinations of 1951, violent skin reactions were frequently seen. Some saw this as an indication that the virulence of the virus might be a factor, but

in judging the skin reaction we must not draw conclusions concerning other reacting parts of the body By this we mean the general immunity and possibly the cerebral reaction Doorschodt pointed this out in judging skin reactions following revaccination.

In England (David) an attempt was made to prevent post-vaccinial encephalitis by dilution of the vaccine, but this proved unsuccessful.

In general it is accepted that there is no sexual predisposition for post-vaccinial encephalitis (Van Bouwdijk Bastiaanse, Meunier) Falk is one of the very few who believe it to be more common in women than in men.

The geographical occurrence shows a very scattered picture. If we consider very large areas, it is observed that post-vaccinial encephalitis is seen mostly in Western Europe, but there are also reports of cases from many other European and non-European (Davies. Africa) countries. Heinsius van den Berg considers the appearance in northern countries more frequent than in southern countries.

If we survey the spread within one country, the findings become less conclusive. Van Bouwdijk Bastiaanse points out that in the 1920's small communities were harder hit than the larger ones, while in Germany Eckstein reports that the larger communities suffered more. The significance of these facts has yet to be discovered

In 1950, Hemmes pointed out the grouping of cases in regard to both location and time He wondered whether some factor may affect a group of the population in such a manner as to lead to the development of post-vaccinial encephalitis, but was unable to explain how this would come about Several investigators (Knöpfelmacher, Keyzer) report a higher incidence in the school years, but we must not forget that the frequency of vaccination in this age-group is a confusing factor We may accept as proven that the risk is much less in the lowest age-group (less than 2 years). Van Bouwdijk Bastiaanse reports a peak of post-vaccinial encephalitis during the months February and March, but this was refuted by other investigators (Heinsius van den Berg, Meunier) The cases we have studied have been spread over the year as shown in Fig 9.

Several times cases of post-vaccinial encephalitis have been reported as having been preceded by head injuries (Schachter. birth trauma, Levaditi and Nicolau, Bickers, Van Bogaert, De Vries) In cases of

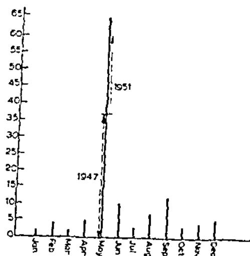


Fig 9. Spreading of our 109 cases of post-vaccinial encephalitis over the year.

recent traumata, we might be able to think in the terms of (to put it very vaguely) a lack of defensive reserve. Another possibility has already been mentioned; that of the sensitization of the cerebrum by the destroyed brain tissue This may offer an explanation as to the pathological-anatomical differences between cases in children and adults. The younger the child, the greater the chance that it has suffered (as yet) no cerebral damage (see Chapter 5) Still another possibility is that we see the reaction of an organ having a locus minorus resistentiae.

The theory of an insufficiency of defensive reserve may well receive support from the fact that post-vaccinial encephalitis is also described following other resistance-lowering circumstances Mage reports a case of post-vaccinial encephalitis seen in a soldier who, after having been to a party, took part in a track meet.

In the Netherlands the following observation was made in two Army battalions The first was given regular duty following vaccination, while the second was restricted to light duty, all other circumstances remaining the same The first battalion showed a definitely higher

rate of reactions, with an increase in the number of neurological symptoms.

Jacobs *et al.* saw a case of post-vaccinial encephalitis following a tooth extraction This was also seen in our material. In the Utrecht Clinic a case was seen following appendectomy which was performed one week after vaccination. The patient recovered completely

The above data serve to suggest that vaccination should be followed by a period of relative rest. In this way the patient's reserves are not wasted on mechanisms other than those that are connected with the production of a successful vaccination.

We have purposely omitted, until now, to mention a phenomenon which is repeatedly reported in the literature: the appearance of more than one case of post-vaccinial encephalitis in the same family. This curious, and not so very uncommon, phenomenon has given us food for thought, especially when one considers the relative rarity of the disorder. It was this phenomenon, among others, which led us to undertake the following investigation.

THE CONSTITUTIONAL FACTOR IN THE ETIOLOGY OF POST-VACCINIAL ENCEPHALITIS: A LITERATURE REVIEW

We examined a number of families in which one or more cases of post-vaccinial encephalitis occurred. (*For description, see Chapter 9*)

The purpose of our investigation was to discover whether or not the occurrence of post-vaccinial encephalitis was determined solely by exogenous factors, and, *if this were not the case*, what *other factors* play a rôle. We were curious as to what rôle, if any, the constitution played in the genesis of post-vaccinial encephalitis. This line of thought was not original. *Earlier reports had pointed in this direction.*

In reviewing the literature we see that in the twenties, Eckstein twice reported the occurrence of two cases of post-vaccinial encephalitis in a single family. It seemed strange to him that a relatively uncommon disease should appear in members of the same family and he therefore published the cases.

Netter (1929) did not feel that the invasion of the central nervous system by a virus was the only factor to be considered in the *etiology* of post-vaccinial encephalitis.

If the central nervous system reacts, there must be a certain amount of susceptibility. This susceptibility would be related to phenomena such as intellectual precocity, surmenage and heredity. In actual fact he pointed in the direction of a constitutional element in the origin of post-vaccinial encephalitis.

In 1929, Brouwer gave a lecture for the 'Medical Circle' of Amsterdam. He discussed the above-mentioned views of Netter and was not enthusiastic about this line of thought. *He expected more results from* experiments with various inoculating material followed by pathological-anatomical control. Luksch, the same year, stated that in addition to the vaccine the disposition of the patient cannot be neglected.

Van Bouwdijk Bastiaanse reported the familial occurrence of post-vaccinial encephalitis.

In 1930, Hutter described various possibilities connected with the problem of the etiology of post-vaccinial encephalitis. If, in one family, we see several cases of post-vaccinial encephalitis within a period of two to three years, then the following possibilities exist:

(1) There is a virus circulating in the family.

(2) There is a familial predisposition.

He claimed that it is the kind of immunity that is important and that this is predetermined and hereditary. It is possible that at the present time weaker constitutional types may be able to live longer and therefore increase the chances of developing post-vaccinial encephalitis. Secondly, that the 'dystrophic diathesis' (intestinal complaints, mucous membrane secretion, serious dermatological conditions) may play a rôle.

All of the above must be studied more intensively, paying special attention to exudative diathesis, lymphatic disposition, neuropathy, rachitic diathesis, spasmophilia, convulsions and persistent enuresis. This, however, cannot be done by one investigator.

In 1932, the *Report of the Encephalitis Commission* appeared. On page 31 we find reference to the occurrence of post-vaccinial encephalitis in grandchildren of two sisters, in one case two brothers and in two other cases two sisters. They also mention that in the Rolleston Report this coincidence is recorded four times They make no definite statement, however, as to whether or not a familial predisposition plays a rôle.

Van Bogaert sees the predisposition in a different light than Hutter. He assumes that if the skin is not able to block the antigen the central nervous system takes up the task This may lead to an encephalitis, but that depends on whether or not there is a congenital or acquired weakness of the hematocerebral barrier (Désensibilisation neurale). In 1937, there was a congress in Belgium which delved into the problem of post-vaccinial encephalitis.

Meunier, in his paper, rejected all suggestion of familial or hereditary predisposition Van Bogaert pointed to several other possibilities He considered the possibility of the existence of a variation of allergic disposition, synchronous with the change of seasons This, in addition

to the individual, familial and racial factor, may give us a better understanding of the problem. As an illustration of possible constitutional factors he cited a case of Couvreur. Couvreur had seen a patient who had exhibited a temporary decline in scholastic ability. During this decline the patient was vaccinated and reacted with a post-vaccinial encephalitis.

Van Bogaert advises that *in children special attention should be paid to neuropathy, convulsions, eczema, status thymo-lymphaticus,* tuberculosis and asthma.

Drogendijk, *in his book Encephalitis Post-vaccinalis,* points out the possibility of a 'certain familial predisposition'. In the same year Comby claimed to see a relationship between *neuropathic heredity* and possible vascular disturbances. *We also see a change of thought in Brouwer, who now says that the vaccine damages the brain only if an endogenous predisposition exists.*

Kokken, *in 1940, shared this opinion when he said: "le virus de la* vaccin n'est pas le seul facteur en jeu mais le terrain joue une rôle primordiale si non unique."

Wigand, in 1942, in an article on encephalomyelitis following German measles, said the following "Da ja in jedem Fall von postinfektiösen Encephalitis das Verhalten des Organismus für die Entstehung des Prozesses von wesentlicher Mitbedeutung ist, werden wir jeder Anomalie des Gesammtkörpers zu beachten haben" Biemond (1946), *in his textbook, described the importance of heredity in post-vaccinial encephalitis and emphasized the importance of recording a detailed familial case history*

*In 1947, mass vaccination was started in the south of the Netherlands. This appeared necessary owing to the spread of smallpox from Belgium. The result was an increase in the number of cases of post-*vaccinial encephalitis.

Later, Keyzer and Nieuwenhuis published an article in which they twice described the occurrence of two cases in the same family. They were, however, still sceptical with regard to *predisposition* They defended this standpoint by stating that the vaccination of 200 feeble-minded patients did not produce a single case of encephalitis

Stuart (1947-48) *recapitulated the theory of an individual familial*

and regional predisposition without throwing any more light on the subject

In 1948, Cornelia de Lange reported a case of post-vaccinial encephalitis in a patient with clubfeet A brother of the patient died of a spina bifida aperta.

Gorter, in 1949, told of a patient whose brother was a mongoloid idiot. He accepted a certain sensitivity in the etiology of post-vaccinial encephalitis but he did not go on to explain this sensitivity.

Doetsch(1949) reported an interesting observation Uniovular twins, 6½ years old, who had previously demonstrated the same reaction-pattern for infections, were vaccinated simultaneously with a younger brother After 13 days one of the twins reacted with an encephalitis. On the grounds of this observation Doetsch tends to accept the theory of a neurotropic virus. In the same year Hofbauer published his experiences with subcutaneous vaccination. Only once did he see encephalitis The child came from a family with many cases of alcoholism and feeble-mindedness According to this author we should accept an hereditary predisposition in diseases of the central nervous system. During the discussion that followed the Congress to Combat Smallpox and Post-vaccinial Encephalitis (Hemmes, Kramer, 1950) Kramer reported two cases of post-vaccinial encephalitis in a brother and sister who had been vaccinated, the one two years after the other He considered the possibility of predisposition playing a rôle (see further)

In 1950, Van Bogaert once again discussed predisposition in an article concerning the para-infectious encephalomyelitis in one of a set of twins The twin sister suffered a meningitis 9 days after simultaneous vaccination.

During the period 1948/49 there were 15 cases of post-vaccinial encephalitis in Stiermarken. Falk (1950) put this sudden increase down to a special neural predisposition of the inhabitants.

In 1952, Hutter repeated his defence for the constitutional factors and pointed to the importance of examining the constitution.

In 1953, André-Balisaux gave a detailed review of the 'facteurs préparants' the gist of which is as follows·

He asks whether we should consider post-vaccinial encephalitis as the activation of an already manifest process in cerebro which is slow

and insidious in growth. He cites cerebral complications following measles and vaccination in patients who were already suffering from diseases of the central nervous system. Or is the problem one of a 'fragilité neurale'? He gathered the following material from the existing literature.

Benvenuti: Patient with post-vaccinial encephalitis. Age 25 months. She was nervous and irritable. Congenital paralysis of the palate and paralysis of the N. Facialis. Grandfather was an alcoholic and mentally strange. Father was a sleep-walker. Brother was an epileptic.

The second case was that of a feeble-minded child suffering from Little's disease. The symptoms of the latter became more severe after vaccination.

Taccone: Family of 12 children. Parents are healthy. Two children died very young. They exhibited premortal convulsions. The patient was the 11th child. At the age of 3 he had convulsions and was mentally retarded. At the age of 13 he was revaccinated and a post-vaccinial encephalitis followed which had a fatal issue The author suggests that attention be paid to familial constitutional factors as well as to previous personal disorders.

Rigotti: Woman, 38 years old. Grandfather on the father's side was placed in a psychiatric institution. Brother exhibited periods of melancholy. The first vaccination took place at a young age During this same period she had measles. At the age of 24: psychiatric treatment; 37: cholecystitis and colitis, 38: after second vaccination the patient suffered an encephalitis which left lasting euphoria and neurologic symptoms

Duken Girl, aged 18 months Nine days after vaccination the patient received a frontal contusio cerebri. The next day she went into a coma, and developed fever and a right-sided hemiplegia. Her father exhibited convulsions after vaccination (at the age of 1).

Besta P 10 years old with post-vaccinial encephalitis. Grandfather on father's side alcoholic Father is very nervous, suffers from chronic headache. Mother is an alcoholic. The patient was vaccinated at the age of 2. Two days afterwards fever and convulsions developed. Encephalitis postvaccinalis (?) Epilepsy as permanent complication.

Rigotti Woman, aged 42. Between the ages of 20 and 23 articular rheumatism. After pregnancy in 1942 patient suffered phlebitis During this period she was vaccinated Six days after vaccination an encephalitis developed Permanent complications developed in the left arm.

Meyer: (1930) Young girl with glomerulo-nephritis was vaccinated. Ten days after vaccination an encephalitis developed.

Da Villa In three cases of post-vaccinial encephalitis the patients were of the tall slender type Two of the patients had an hereditary taint (tuberculosis and alcoholism in the family).

Alberto Mugio (1925)· Two children suffering from spasmophylia developed encephalitis post-vaccinalis.

Da Villa Boy, 8 years old Father suffered from delirium tremens with suicidal tendencies Patient: asthenic, adenopathy, tracheo-bronchitis, micro-polyadenitis and laryngospasm. Following vaccination an encephalitis developed with hallucinations. Healed completely

André-Balisaux writes "Certaines déterminations rheumatismales, vasculaires, renales doivent être retenues, comme elles l'ont été par Van Bogaert dans ses recherches sur les déterminations encéphalitiques des exanthemes et de certaines encéphalites dites allergiques, sans qu'on puisse encore actuellement se prononcer sur la valeur de leur incidence. On peut évidemment contester statistiquement leur signification nous les invoquons ici dans l'ignorance ou nous sommes encore d'un méchanisme physio-pathologique de ses accidents sans plus "

Daser Brother and sister vaccinated simultaneously Both children died, 12 and 14 days later.

Kramer (1925/26) A family with three children. In 1923, a girl died of a tubercular meningitis following vaccination This could very possibly have been an encephalitis post-vaccinalis In 1925, her 6-year-old brother died of post-vaccinial encephalitis

Fanconi Eight-year-old boy At the age of 4 months the infant had chicken-pox and a commotio cerebri Twelve days after vaccination an encephalitis developed A brother, age 12½, who had suffered from enuresis nocturna until his 12th year, was vaccinated three days later with a different vaccine On the 14th day he developed an encephalitis Both children recovered. According to the author, the commotio cerebri sensitized the vasculo-vegetative system In this regard he said "on sait combien les énuresies sont frequemment les temoins d'une épilepsie infraclinique ou non reconnue" This may hold true for some patients but certainly not for all

The material investigated by André-Balisaux himself was as follows:

Family van G. The eldest child, a 13-year-old boy; encephalitis post vaccinialis. As a permanent complication there were disturbances in the electro-encephalogram. The second patient was a boy of 10. After post-vaccinial encephalitis he too showed changes in the electro-encephalogram. The third boy was not vaccinated. He had a normal encephalogram. Father: healthy. Mother: fragile, nervous, with tendencies to anaemia.

Family G. Eldest child: Male, 30. Congenital bilateral deafness.
Second: Female, 29. Normal
Third: Male, 28. Pleuritis.
Fourth: Male, 22. Post-vaccinial encephalitis.
Fifth: Male, 20. Right-sided deafness.

The first, third and fourth were vaccinated at an early age. The fourth developed an encephalitis following revaccination. The following is his personal history:

Three months old: chickenpox. Seven years old: nephritis following scarlet fever. Healed. At the age of 22 he was revaccinated and developed an encephalitis which left permanent electro-encephalogram changes. The third and fifth had electro-encephalograms that bordered on the abnormal.

André-Balisaux thinks it possible that before the fourth was vaccinated, slight changes had already existed in the electro-encephalogram as an expression of neural sensitivity; the encephalitis accentuated the changes. The following conclusions were drawn from the above:

(1) The patients did not exhibit a more than normal allergic or vascular disposition.

(2) Predisposing factors are:

(a) Somatic trauma.

(b) Psychic trauma (probably originating as a result of vascular changes or changes in the equilibrium between the endocrine and autonomic system).

(c) Toxic-infectious conditions.

Under (a) are taken into account factors such as cooling, overheating, etc. Owing to changes brought about in the permeability of the vascular system, these factors can be fatal during critical periods.

(3) Owing to the simultaneous occurrence of the predisposing and preparatory factors, a sensitization of the central or peripheral

nervous system arises This paves the way for the so-called 'neuro-allergic reaction'.
(4) Recurrences are very rarely or never seen, thus a very strong immunity must exist. This last conclusion is difficult to support. Once a patient has suffered an encephalitis post-vaccinialis a re-vaccination is generally not indicated (see page 127).
(5) It is strange that other processes play a rôle in the sensitization of the cerebrum The author (A -B) of the opinion that an infection can bring about two separate conditions. The first is a specific immunity. The second, a 'parallergic', which carries the reaction possibility in it for diseases in the same group
(6) The electro-encephalogram may be able to tell us something of the future reactions.

The degree to which the observations of André-Balisaux support the above remains to be seen

The description of the clinical phenomena, especially if one examines the incubation periods, indicates that care must be taken in many cases before drawing concrete conclusions. If these investigations are to be valid we must be strict in our choice of material. We feel that a more complete examination is necessary. Without this an accurate evaluation is, in our opinion, impossible.

In reviewing the literature we found an article by De Morsier (1955) that reported an observation made by Guttmann A 5-year-old child suffered an encephalitis post-vaccinialis that was followed by a hemiparesis It also became subject to epileptic fits As treatment for this complication an operation was performed which proved fatal. At autopsy the corpus callosum and the vermis cerebelli were absent. Both of these defects are classified under the heading of cranio-encephalic dysraphia.

In reviewing all of the material in the literature we are struck by the frequent reference to constitutional factors, which may play a rôle in the etiology of post-vaccinial encephalitis In our clinic we also observed tendencies in this direction In our out-patient department we saw a case in which a child has secondarily infected her mother with vaccinia virus Both mother and child suffered a post-vaccinial encephalitis The mother retained symptoms of diencephalic

disregulation as a permanent complication. The family history showed the following peculiarities:

S 1 M: aged four, profuse bleeding from nose and kidneys

S 2 M, *S 3 M* and *F M:* enuresis nocturna. *M*, enuresis nocturna until the age of 10. Spina bifida occulta.

S P: Bilateral clinodactyly of the 5th digits and sacral hairgrowth

A second case was as follows:

Family v. d. V. Parents and seven children wanted to emigrate to Canada. Vaccination of the entire family was necessary. The parents had been vaccinated previously but not so the children. The oldest child, a boy of 14, was admitted to our clinic. On the 12th day after vaccination he developed an encephalitis. We found that, in addition to the encephalitis, the child had glomerulo-nephritis. Both conditions disappeared completely On the 15th day after vaccination we examined the entire family. *P.* On the 8th day after vaccination had a headache and temperature of 40 6° C. Emotional lability followed. Felt apathetic. During examination the patient impressed us as being feeble-minded. The patient had a right-sided Babinski-reflex and dubious Gordon and Oppenheim reflexes *M:* No complaints following vaccination. Examination: slight funnel chest and clinodactyly. *F 1·* Age 12 years. Ten days after vaccination had fever. Examination: Thorax "en Bateau". High right shoulder. Positive Oppenheim and Gordon reflexes on the left *S 1·* Age 9 Seventh day after vaccination had a temperature and headache. Examination: slight funnel chest. High palate. Right shoulder higher than the left. No neurological symptoms. *F 2.* Age 8 Seventh day after vaccination fever. Examination: Slight funnel chest. No neurological symptoms. Patient is most probably feeble-minded. Cannot attend normal school. *S 2.* Age 6. Was ill from the 5th to the 7th day following vaccination. Felt better for two days but on the 9th day again became ill High temperature and headache. Examination· Bilateral clinodactyly No neurological symptoms *S 3* Age 5. Cranky and listless after vaccination Examination Impressed us as being feeble-minded. Speech retarded Enuresis nocturna No neurological symptoms *P M* died at the age of 66, of a heart attack *M M* died at the age of 55. Apoplexy was clinically diagnosed Suffered frequent nervous break-downs *F 1 M* and *F P* were both in psychiatric institutions. *F 2 P·* hydrocephalus

Conclusion In the family of a patient with post-vaccinial encephalitis we were able to find neurological symptoms in members other than the patient This examination took place 15 days after vaccination The family exhibited a familial burden in the form of signs of the status dysraphicus and psychiatric disturbances.

CONSTITUTION AND ELECTIVITY IN INFLAMMATORY PROCESSES OF THE CENTRAL NERVOUS SYSTEM

In 1952, Sillevis Smitt published his article "The prevention of post-vaccinial encephalitis". He discussed whether one could prevent a large number of post-vaccinial complications by carefully selecting patients for vaccination. In view of the fact that so little concrete information has been obtained after all these years of investigating the exogenous factors, Sillevis Smitt suggests further study in the direction of the endogenous factors He writes: "From everyday clinical experiences it appears that all inflammatory processes of the central nervous system under which falls encephalitis are actually 'Auslese Krankheiten'. The frequency is determined by the concept of 'electivity', since we see only a small percentage of those exposed to the infection actually falling ill."

We see very few cases of encephalitis following measles just as we see very few cases of chorea minor following rheumatic fever This makes us feel that in addition to the exogenous factor an endogenous predisposition plays a role. We see this in the literature and it is more or less evident in our own experience. It is, therefore, probable that this predisposition determines whether the nervous system will be involved in the disease process. This view was also expressed by Pette in 1929.

He pointed out that investigation of acute infectious diseases of the central nervous system has yielded results with regard to the causative agents, yet the problem of the pathogenesis has not been solved He feels it to be necessary to consider the endogenous influences in order to gain further insight into this problem He stressed this when he discussed post-vaccinial encephalitis In 1933, Curtius published *Multiple Sklerose und Erbanlage* In this work he discussed the genesis of multiple sclerosis from the endogenous point of view, *e g.*

the hereditary factors. In this way he drew a parallel between the pathogenesis of multiple sclerosis and post-vaccinial encephalitis This approach involves the constitution and on this subject an extensive mass of literature exists. It does not lie within the scope of the present work to go into this in detail (see the work of Sillevis Smitt and Kuiper). However, in order to understand the concept we are discussing we shall try to define it in brief.

The idea of constitution is very old. At first it was a very static concept in which every individual possessed a definite constitution With Hypocrates we see the concept of constitution acquiring a more dynamic aspect. Through the mixing of the four body fluids, yellow and black bile, mucus and blood, the health of the individual is determined. If the correct ratio exists between these substances we speak of eucrasia. If this is not the case then we speak of dyscrasia

We do not intend to follow the complete development of the constitutional way of thinking. One thing is certain and that is that the more 'causes' of diseases were discovered, the less importance was attached to the constitution.

In the past several years the laboratory diagnosis has made such enormous advances that the concept of constitution is no longer considered when searching for a diagnosis. What do we now understand by constitution?

Every individual originates through the union of two sex cells The fertilized egg that results carries with it a certain number of chromosomes. These are the material carriers of properties and form the 'basic material' from which is determined what potentials the developing individual will possess. They form what is generally called the genotype. As soon as the individual begins to develop there appear, besides the hereditary factors, the exogenous factors These will determine which of the hereditarily acquired factors will become manifest, i e what will become of the phenotype. These influences, also called the 'milieu', determine how the individual will present itself The milieu does not begin after birth; it has an important role in the embryonic stage

Wortman gives the following description: "The more that life advances the more the phenotype takes over the genotype until death makes of the genotype an absolute phenotype." In a review of

development Stockard comes to the following conclusion: "Without a genetic basis there is no individual and without a suitably arranged complexity of environment the complete genetic basis is unable to produce the normal individual".

If we regard the adult individual according to his appearance and his reaction possibilities then we are forced to consider both components separately If we consider the constitution we encounter the same problem The outward reaction of an individual to stimuli is determined by the genetic make-up and the changes made by the milieu There are two alternatives·

(1) These reaction possibilities, determined by endogenous genetic and milieu factors, are called constitution.

(2) The concept 'constitution' is reserved for the part of the genotype. Julius Bauer described this as "the sum total of an individual's characteristics as they are potentially determined at the moment of fertilization".

Peust described the constitution as "der Ausdruck fur die spezifische Art der biologischen Beschaffenheit seines Trägers, mit dem Leben, seinen Widerstanden und Schädlichkeiten fertig zu werden und bildet damit zugleich den konkreten Ausdruck fur die korperliche, geistige und seelische Erhaltungsfahigkeit ihres Tragers".

If we take into account the changes of the reaction pattern as brought about by the milieu then we speak of the 'condition'. In this last case we can also speak of 'pheno-constitution' We can then consider the concept 'constitution' as described by Peust, by the word 'geno-constitution'. The pheno-constitution is partly expressed by the morphological appearance and also by the reaction pattern of the individual In this respect we have to keep in mind that every reaction which takes place does so not solely through the condition but that at the same time the reaction changes the condition in a more or less characteristic way In this way the reaction to a disease-producing agent will be determined by the pheno-constitution. After this reaction, the individual can react to the identical stimuli in a different manner It is obvious from the above that the whole of the function and form exists in a close harmony This close connection is also expressed in Kretschmer's *Körperbau und Charakter* He writes: "Das Problem Form und Funktion steht vom ersten Beginn hinter

unseren Untersuchungen über die korrelativen Zusammenhänge der psycho-physische Persönlichkeit. Form und Funktion sind keine Gegensatze, sondern zwei Aspekte derselben Sache."

In the pheno-constitution or condition we also see an expression of the basic geno-constitution. We can, therefore, expect that by examining families with regard to constitutional make-up we shall find many similarities in both form and content. These can be the determining factors in the origin of predisposition In other words, it is this inheritance on the part of an individual that gives a pathological process its chance for development. We can theoretically classify pathological reactions as follows (Polman):

(1) Reactions principally determined by hereditary factors
(2) Reactions principally determined by the milieu
(3) Reactions determined by the equilibrium between genes and milieu.

It is self-evident that transition forms exist. On these grounds, Polman came to the conclusion that it is impossible to make a sharp distinction between hereditary and non-hereditary diseases Every individual reacts to an external agent in a manner characteristic of his particular genetic make-up. This same idea is found in the inaugural address of Biemond. Even in diseases that are known to be determined principally by heredity we see an equilibrium between genetics and the milieu. In this regard Biemond gave a splendid example He also points out that it is impossible to speak of homology and homotypes in neurology for the following reasons:

(1) The geno-type may not be completely developed (inadequate expression)
(2) Some syndromes need a specific genetic composition. This acts as a source of great variety.
(3) A gene can sometimes express itself in many different ways as in Wilson's Disease (central nervous system, liver and cornea) This is the so-called pleiotrophism In this way the homology and homotype are surpassed by the heterology and the heterotype. This is expressed by Kroll when he said 'das a-typische wird typisch'. Curtius, when considering the heteropheny in inherited neurological diseases also pointed [illegible] the impossibility of a sharp distinction in this area. Accordi[illegible] Curtius, we must view the occurrence of real 'Umwelt-

bedingte' diseases in families with hereditary, organic (neurological) diseases in such a way as to take into account the hereditary disposition. This disposition is closely related to the inherited defect of the 'Anlage' of the central nervous system. Biemond points out that all of this lies within the area of preventive medicine. We are concerned with recognizing the basis on which certain noxae get their chance to develop. Sillevis Smitt stressed the importance of the constitution in the genesis of post-vaccinial encephalitis.

We have seen that many years of searching for exogenous factors has not yielded the expected results. We have no convincing theory concerning the genesis of the disease. We only know that occasionally after vaccination there is a reaction on the part of the central nervous system and that this nervous system belongs to a reacting individual. Is it surprising therefore that we should approach the problem from a different direction and now ask what constitutional properties are to be observed in a patient with post-vaccinial encephalitis? This is an attempt to discover the conditions which make one susceptible. We must realize that the constitution is not the only other factor besides the vaccine. The condition of the vaccinated person probably plays an important rôle (see Chapter 6).

Resistance will be met from those people who feel that trying to approach the problem in a constitutional way will discourage advances in therapeutic directions. This will happen because of the premise: "It is constitutional, thus little can be done". We definitely do not believe this. On the contrary, we believe that if our therapy be rational then we have to consider the constitution within our frame of reference. If we do not do this our therapeutic results will definitely suffer.

The study of the influence of constitutional factors in neurological diseases has previously been carried on in other cases. We mentioned the work of Curtius with multiple sclerosis. He compared the findings in families of patients with multiple sclerosis with a control group. He found significant differences with regard to stigmata in these two groups.

If we review the various stigmata in the reported investigation we are impressed by the heterogeneous picture. We find properties whose importance is not fully understood. In this regard we should like to point out the danger of putting too much emphasis on symptoms

whose value cannot, at present, be assessed. Wagner von Jauregg gave a warning after the work of Curtius appeared. This was especially against the exaggerated importance given to heredity examination. Curtius also reported constitutional factors as playing a rôle in tabes dorsalis.

The problem of the constitution has also been spoken of in relation to encephalitis epidemica. Stern, however, denies that it plays a rôle. Villinger (1921), Peust (1924) and Klaus Jensch (1939) conducted an investigation and came to the conclusion that before one acquires encephalitis epidemica a predisposition has to exist.

Curtius points out that in the examination of the constitutional factors special attention must be paid to the following points:

(1) A special topical disposition.

(2) A general neuropathic constitution.

(3) An extra-neural disposition.

The topical disposition is very often seen in a particular family reaction pattern. We see families that suffer from a high number of changes in the strio-pallidar system. Curtius reports the predisposition for diseases in the anterior motor cells. He points out the combination of poliomyelitis anterior acuta and Duchenna-Aran's Disease. We have seen a patient who during his youth had suffered from poliomyelitis anterior acuta and at a later age developed the picture of amyotrophic lateral sclerosis. We have not been able to demonstrate from the available information a topical disposition of the white matter (this is the area in which the post-vaccinial encephalitis occurs)

We have attempted to find a general neuropathic constitution and, as far as possible, to demonstrate an extra-neural disposition. The concept 'neuropathic constitution' has grown during the last century.

In 1857 the work of Morel *Traité des Dégénérescences* appeared. He introduced the concept 'degeneration' into the medical field, especially in psychiatry. Féré (1894) then launched the idea of 'la famille neuropathique'. He described in various families a high percentage of neurosis, psychopathy and criminality. He pointed to the correlation that existed between neurological diseases and the so-called 'stigmata degenerationis' and linked in this way degeneration with neurological changes

Looking over the so-called stigmata, which are considered to be

indicative of a defective constitution, we are confronted with a strange picture. To get an idea of how the problem of heredity was approached in those days we have only to consider that Féré felt that coitus after a funeral would result in an individual who was basically depressive. A long way had to be travelled before these concepts could be considered in a scientifically responsible manner.

It was Bremer and Curtius who succeeded in putting the relationship between the stigmata degenerationis and neurological changes into a systematic order. This line of thought was introduced to the Netherlands mainly by the work of Sillevis Smitt.

How do these stigmata originate? It is generally accepted that they occur through mutations. These mutations cause the majority of changes in the places where sensitivity is the greatest Since the sensitivity to changes in the milieu is greatest where the differentiation is the furthest, it is not surprising that we can observe the results of the changes so manifold in the area of the central nervous system.

The resulting tendencies, being genetically bound, are passed on to the following generations. In this way we can see individual constitutional properties manifesting themselves as familial ones.

In our examination we have paid special attention to.

(A) *Morphological changes.*

(1) The classical heredo-degenerative disease pictures These are progressive during lifetime.
(2) Macro-heredo-degeneration These conditions of prominent degenerative syndromes are constant throughout life.
(3) The stigmata degenerationis or micro-degenerations Under this heading fall the stigmata of the status dysraphicus (Bijl)
(4) Other neurological pictures (epilepsy, etc.)

(B) *Endocrine-diencephalic disturbances*

The endocrine system is centrally regulated by the hypothalamic-pituitary system. This area is functionally and anatomically in very close contact with the rest of the central nervous system We considered it advisable to give the endocrine system a place when we studied the aberrations of the central nervous system

(C) *Vegetative regulation disturbances.*

These are difficult to determine by examination at an out-patient clinic. Only with very clear-cut changes and reliable case histories was it possible to evaluate vegetative disturbances.

(D) *Allergic stigmata.*

In view of the fact that there are many investigators who accept an allergic genesis of post-vaccinial encephalitis, we considered it desirable to draw special attention to allergic stigmata. This was done in the first place with the goal of finding out whether a correlation exists with the 'allergic predisposition' of the nervous system, and secondly because these conditions are a part of the concept 'neuropathic constitution'.

If we take groups B, C and D together then we see that disturbances in one of these groups very often coincide with disturbances in the other groups. The function of the endocrine system is very closely tied up with the vegetative nervous system. We see this in everyday physiological mechanisms. The 'day rhythm' shows a very close relationship between the two (Gathier). Also in all of the physiological and pathological changes that take place in the endocrine system we see changes occurring in the vegetative system. During pregnancy an increased reactibility exists on the part of the vegetative nervous system The symptoms of vegetative lability during the climacterium are well known, just as we are all familiar with vegetative reactions during hypoglycaemia and thyreotoxicosis Hess demonstrated this relationship experimentally in animals. He made use of electrical stimulation in the area of the tuber cinereum.

A relationship is generally accepted between allergic disturbances and the vegetative nervous system. Berger and Hansen write. 'Bei dem grossen Anteil, den das Gefässsystem an der Allergisierung nimmt, ist es verständlich, dass die schon vor dem ersten Allergenkontakt gegebene, ererbte oder erworbene, allgemeine und örtliche Gefässverfassung an der Disposition zur Allergisierung hervorragenden Anteil hat. Es ist in der Tat eine alte ärztliche Beobachtung dass gefässlabile, gefässeretische, vasomotorische, angioneurotische Men-

schen bevorzugt allergisch sind, wenngleich natürlich – auch nach eigener Untersuchungen uber die interkutan prüfbare Gefasserregbarkeit – diese besondere Gefassdisposition nicht obligat ist".

We have not grouped migraine under the allergic disturbances because of the doubt that exists regarding its validity. We see various forms of migraine occurring in the same family.

Van der Does de Willebois considers the allergic genesis of migraine as probable and believes a special equilibrium condition of the neurovegetative system to be prerequisite for its origin

We shall consider it as an accepted fact that changes in the endocrine system exert an influence on migraine. In 1952, Schwartz published a study titled *Heredity in Bronchial Asthma*. In it correlations are made between different allergic disturbances He found a positive correlation between migraine and urticaria. Further correlations were not such as would place migraine in the group of allergic diseases From his findings it would appear that there is most probably no direct connection between migraine and bronchial asthma.

Other diseases that are considered by many authors to be allergic in origin are discussed separately below. This is done because their allergic origin has not (yet) been proved. The skin diseases ichthyosis and psoriasis fall in this group.

Ichthyosis is often seen in patients suffering from Besnier's prurigo and/or bronchial asthma Although the etiology of ichthyosis and its connection with allergy is still unknown, many attach significance to the fact that it occurs with the above-mentioned diseases. Another point of view is that diseases of the skin, which are seen in families with allergic syndromes, though they in many ways resemble ichthyosis are not identical with it In these cases perhaps it would be more correct to speak of dry hyperkeratotic skin.

Another problem connected with ichthyosis is the frequent occurrence of neurological, psychiatric and endocrine diseases in the same family Laubenthal points out that, in addition to changes as shown in the above-mentioned conditions, there are also changes in the body structure. In general, the body build of the patient is of the asthenic type Laubenthal points out that changes occur in what he calls the acrale growth By this he means the short fingers (brachydactyly),

excessive growth of the acra in the form of arachnodactyly, too many fingers (polydactyly) or changes in the growth of the jaw. Laubenthal considers the essential disturbance to be a change in the pituitary-diencephalon area The frequent occurrence of neurological diseases in the form of striatum changes would subscribe to this opinion. Psoriasis is sometimes seen in combination with hay-fever. Schwartz points out that psoriasis is very seldom seen in combination with other allergic diseases and also that the pathological anatomical study of the disease is not such that we can be certain about its allergic origin. Polyarthritis rheumatica chronica and polyarthritis rheumatica acuta have recently been placed in the group of the allergic diseases.

Up till now there is no certainty about whether or not allergy plays a rôle. Examination of a large group of patients with the disease has not resulted in a correlation between it and the well-known allergic syndromes (Järvinen) There is, according to some, a positive correlation with migraine (Traut and Vrtiak)

In addition to the above-mentioned skin conditions, attention was paid to other dermatological changes. We recorded all pigment anomalies such as depigmentation, 'café-au-lait' spots and pigmented naevi. These anomalies are well-known in the phacomatoses; however, we see phenomena that are not connected with these diseases.

The pigment-carrying cells are ontogenetically derived from the neural crest. Parts of the vegetative nervous system originate in the same area. We can easily imagine that disturbances in the development of the nervous system, such as status dysraphicus (Bijl), may coincide with changes in the pigment distribution of the skin

We were also interested in vascular anomalies (haemangiomata) as a form of the stigmata degenerationis. Status dysraphicus plays an important rôle in our consideration of the constitution

As far as was possible with an out-patient examination, these constitutional, dysontogenetic factors were recorded. It was not possible to complete our findings by radiological examination Our findings in this investigation also include individual aberrations that are due to the so-called phenocopies

The effect of the above does not alter our final conclusions since we have concerned ourselves with family histories and therefore the isolated individual stigmata are incorporated in the sum of the

genealogical tree Besides, we shall also see the phenocopies in our control group

There is no reason to believe that the frequency of phenocopies should be different in both groups. The stigmata of the status dysraphicus as recorded in our investigation are in accord with the findings of Bijl For an outline of the data compiled by us we refer the reader to the following chapter We emphasized the status dysraphicus because a correlation exists between this constitutional disposition and a greater or lesser inferiority of the central nervous system (Curtius, Sillevis Smitt, Bijl) In our consideration it is not possible to draw a sharp line between the status dysraphicus and, on the one hand, the normal condition, and, on the other hand, further abnormal constitutional types Sillevis Smitt pointed to the relationship of the status dysraphicus and the phenomenon of arachnodactyly.

Furthermore, we are aware of the dysraphic stigmata and the diencephalosis (Sillevis Smitt, Kuiper) Here we see a trait d'union between the status dysraphicus and endocrine and vegetative stigmata Other relations can be found in the literature For a more detailed survey we refer the reader to the work of Bijl We should like to point out one such relationship Bremer, Curtius, Kehrer and Sillevis Smitt, from their clinical experience, pointed to the connection of the status dysraphicus and mental instability This was checked statistically in a group of Dutch recruits by Bijl He too found a correlation between the above-mentioned conditions

Attention was also paid to fibromata, fibro-lipomata and many other conditions called 'stigmata degenerationis'

In addition to the above we recorded, as far as possible, all the peculiarities concerning internal organs as well as causes of death

It is not possible to discuss all the implicated symptoms separately, we refer to Chapter 9 containing the results and conclusions of our investigation

CONSTITUTION AND PREDISPOSITION IN POST-VACCINIAL ENCEPHALITIS

The investigation into constitutional factors predisposing to post-vaccinial encephalitis was based on the cases reported to the Netherlands Chief Inspectorate of Public Health during the period 1945 through 1951. From this material we selected such cases as could be classified in groups 1 and 2 of the classification given on page 30. Whenever possible, examinations included the patient and his brothers and sisters, the parents and their brothers and sisters, and the grandparents. With regard to the cousins, only anamnestic data were collected.

Unfortunately it was impossible to include all the patients registered during the above-mentioned period because some families refused to cooperate. On the other hand, the investigation was facilitated by the following favourable factors:

(1) The incidence of post-vaccinial encephalitis in the Netherlands was high in the above-mentioned period.

(2) Distances in the Netherlands are so limited that it was possible to visit nearly all relatives, even when scattered throughout the country.

(3) The rate of emigration from the Netherlands is relatively low.

The investigation covered 107 families, including 109 cases of post-vaccinial encephalitis. Encephalitis occurred in the same family in two instances. In one instance the diagnosis was made in two cousins (their mothers were sisters). One case of encephalitis was in a child of an unmarried mother. The geographic distribution of the 107 patients was as follows

Aarle Rixtel	1	Apeldoorn	1	Bergentheim	1
Amsterdam	5	Arnhem	1	Berkel (Z.H.)	1
Amersfoort	1	Assen	2	Blerick	3

Bloemendaal	1	Helmond	1	Oude Pekela	1
Breda	2	Helvoirt	1	Roden	1
Cuyck	1	Hilversum	1	Roermond	1
Drunen	2	Hoeven	1	Rotterdam	6
Eindhoven	1	Kerkrade	2	Rijnsburg	1
Enschede	1	Kollum	1	Schinnen	1
Fijnaart	1	Menaldumadeel	1	Sevenum	1
Geertruidenberg	1	Moergestel	1	Sneek	1
Gemert	1	Musselkanaal	1	Steenwijk	1
Gouda	1	Naaldwijk	1	Tilburg	23
Grotebroek	1	Nijeveen	1	Udenhout	1
Den Haag	5	Nijmegen	3	Utrecht	2
Haaren	1	Oirsbeek	1	Voorburg	1
Haarlem	2	Oirschot	1	Voorhout	1
Halsteren	1	Oosterbeek	1	Zaandam	1
Heemstede	1	Oosterhout	2	Zeist	1
Den Helder	3	Oosterwolde	1	Zevenaar	1
				Zuilen	1

The patients were 70 males and 39 females, with the following age distribution

0–2 years	26	10–20 years	39
2–5 years	5	20–30 years	23
5–10 years	14	40–50 years	2

The 107 families included 107 mothers and 106 fathers, *i.e.* a total of 213 parents. Owing to the above-mentioned facts, the number of grandparents was limited to 424. The total number of subjects (patients and relatives) included in the investigation was 2,484. This group will henceforth be referred to as the encephalitis group.

The grandparents' generation is referred to as the A-generation, that of the parents as the B-generation and that of the patient as the C-generation. The B-generation included a total of 1,449 subjects, and the C-generation 611.

The manner of examination of testees was recorded as

(1) Complete. The completest possible examination was made in the out-patient clinic.

(2) Partial. These subjects refused to undress completely but consented to an inspection of the head, hands and feet.

(3) No examination but only collection of anamnestic data, verified as much as possible via medical agencies.

	Completely examined	*Partially examined*	*Anamnestic data only*
A-generation	79	21	324
B-generation	820	86	543
C-generation	438	32	141

Verification of the results of our investigation would actually require comparison with the average values in the Netherlands.

Some large-scale investigations into the incidence of various manifestations in the average population have been made abroad (Luxenburger, Strömgren and others) but no effective data of this type were available for the Netherlands. It was therefore necessary to furnish comparative material which could be regarded as more or less representative of the average Dutch population. In collaboration with Van der Wiel, who made a similar investigation among relatives of patients suffering from a cerebral tumour, 102 families were studied, again including three generations. Fifty families were investigated by Van der Wiel. His starting-point for the control group was a random proband who corresponded with the cerebral tumour patient as to age and occupation

Our control group was composed in a different manner. We selected the first families listed under each letter of the alphabet in the civil registry of the municipality of Utrecht. Utrecht is a medium-size city in the central region of the Netherlands, with an exceedingly mixed population, and panmixia can be assumed by approximation These two groups will henceforth be referred to, collectively, as the 'control group', whereas the Utrecht group will be called the 'own control group'.

Van der Wiel's control group showed the following composition:

	Total number	*Completely examined*	*Partially examined*	*Not examined*
A-generation	200	35	0	165
B-generation	526	342	0	184
C-generation	245	214	0	31

The distribution in our own control group was as follows

	Total number	*Completely examined*	*Partially examined*	*Not examined*
A-generation	208	84	8	116
B-generation	558	335	13	210
C-generation	129	122	0	7

The control group included a total number of 1,866 subjects, of whom 895 were included in our own control group.

The graphs of Fig 10 (p. 88) give an impression of the age distribution in the groups at the time of investigation, according to generation and sex For fatal cases the age at the time of death was recorded

This figure shows that the distributions in the A- and B-generations are not widely different. The C-generation, however, shows a more marked difference in that older age is predominant in the control group Our own control group shows a slight shift in favour of younger age

Table 2 (p 90) shows a division in the groups according to family size. Family size denotes the total number of subjects in the three generations.

This table clearly shows that the encephalitis group includes a larger number of large families than the control group In view of the higher age average in the control group it is possible that symptoms becoming more marked with increasing age are more readily diagnosed in this group because they have had time to develop If a higher frequency is none the less found in the encephalitis group, then this difference is only emphasized by the above-mentioned circumstances

Since this investigation was instituted in order to detect familial hereditary factors, the familial correlation of individual findings must not be neglected in interpreting results We are concerned with familial features rather than with individual data Individual data in both groups can be compared only if the following requirements have been met

(a) Corresponding age distribution, and

(b) Corresponding family sizes

It is difficult to meet these requirements, particularly in a relatively

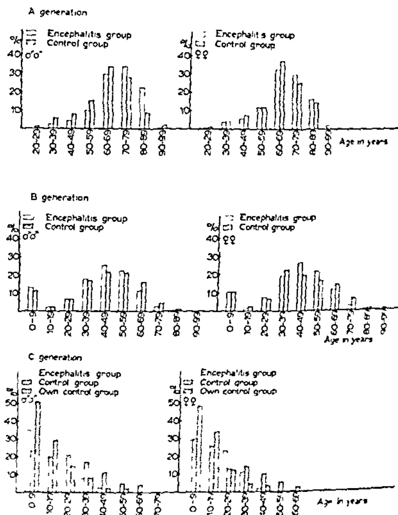


Fig 10 Age distribution (in percentages)

small group such as this. In so far as possible, corrections were applied in the elaboration of results to enable a statistical approach. Whenever there was no such possibility, there being a risk of excessive mutilation of the material, the findings obtained were used as an illustration of more or less obvious clinical observations. This would seem to us to be preferable to complicated statistical procedures which only seemingly elucidate the subject.

In the following sections a survey is given of the various deviations and anomalies observed in the course of the investigation or included in the anamnesis.

Whenever comparisons are made between percentages of tainted families in distributions according to family size, those percentages that have been derived from groups smaller than 10 families are presented in italics to denote a higher degree of unreliability.

Diseases of the central nervous system (including the meninges)

A striking feature in the results of this investigation reproduced in Table 3 (p. 90) is that the two groups do not differ much in the total number of affections of the CNS. When the inflammations and inflammatory disorders (the groups I of the encephalitis and the control group) are separately regarded, however, the encephalitis group is seen to include twice as many families with one or several of such anomalies as the control group.

This proportion indicates that the families of the encephalitis group have an increased tendency to react by inflammations and inflammatory changes in the CNS.

Peripheral neurological disturbances

In respect to the figures of Table 4 (p. 92), too, the incidence of disturbances in the encephalitis group is unmistakably higher than that in the control group. In the latter group, the data on the own control material are the least unfavourable, even in comparison with these data, however, the figures obtained are as follows:

Encephalitis group: 35 disturbances in 27 out of 107 families
Own control group: 10 disturbances in 10 out of 52 families

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	2	—	12	—	23	—	20	—	33	—	17	—	107	—
Control group	3	—	20	—	40	—	26	—	10	—	3	—	102	—
Own control group	3	—	14	—	19	—	9	—	6	—	1	—	52	—

TABLE 3 DISEASES OF THE CENTRAL NERVOUS SYSTEM (INCLUDING THE MENINGES)

ENCEPHALITIS GROUP

I. *Inflammations and inflammatory disorders*

Encephalitis		
After German measles	2	
Von Economo	1	
Post-vaccinial	1	
Other forms	5	total 9 (in 9 families)
Meningitis (non-tuberculous)		15 (in 15 families)
Poliomyelitis ant ac.		4 (in 4 families)
Myelitis		1
Multiple sclerosis		1
Tabes dorsalis		1

II. *Other disorders*:

Morbus Parkinson		5
Chorea minor		1
Tremores:		
congenital (?)	3	
other	2	total 5
Tumor cerebri		
Morbus Little		

Syringomyelia		–	
Spastic manifestations e c i		5	
Congenital encephalopathy		1	
Cerebellar ataxia		1	
Arachnoid haemorrhage		1	
Total number of anomalies (group I and II)		56	(group I) 31
Spread over		43 families	29 families

ONTROL GROUP

Inflammations and inflammatory disorders			
Encephalitis			
Von Economo	2(1)		
Other forms	1(1)	total	3(2) (in 3(2) families)
Meningitis			
Tuberculous	1(0)		
Other forms	6(5)	total	7(5) (in 6(4) families)
Poliomyelitis ant ac			1(0)
Multiple sclerosis			1(1)
Cerebral abscess			2(0)
er disorders			
Morbus Parkinson			6(4)
Chorea minor			1(1)
Tumor cerebri			1(1)
Morbus Little			1(0)
Spastic manifestations e c i			6(6)
Narcolepsy			1(0)
Post-traumatic encephalopathy			1(0)
Hereditary spastic spinal paraplegia (in 1 family)			7(7)
Total number of anomalies (group I and II)			38(28) (group I) 14(8)
Spread over			29(20) families 13(7) families

The number in parentheses refers to our own control material

TABLE 4 PERIPHERAL NEUROLOGICAL DISTURBANCES

ENCEPHALITIS GROUP

Trigeminal neuralgia			1
Bell's palsy			1
Polyneuritis (after diphtheria)			3
Herpes zoster			3
Paresis of the ulnar nerve			1
Scalenus syndrome			1
Meralgia paraesthetica			2
Torticollis			1
Myotonic manifestations			1
Adie's syndrome			1
Areflexia of the legs			2
Neurogenic dystrophy of the muscles	2		
Areflexia in the same family	4	total	6
Intervertebral disc protrusion (in 11 families)			12
Total number of anomalies			35
Spread over			27 families

CONTROL GROUP

		Own controls
Trigeminal neuralgia	1	1
Bell's palsy	1	1
Neuritis of the ischiadic nerve	1	1
Neuritis of the brachial plexus	1	1

Herpes zoster	1	1
Partial thenar atrophy	1	1
Areflexia of the legs	2	2
Intervertebral disc protrusion	5	2
Total number of anomalies	13	10
Spread over	13 families	10 families

TABLE 5 PSYCHIATRIC DISTURBANCES

	Encephalitis group		Control group		Own control group	
	Number	Number of families	Number	Number of families	Number	Number of families
Institutionalized or been institutionalized						
Schizophrenia	2	2	2	2	0	0
Manic depressive group	3	2	0	0	0	0
Other psychoses	30	25	14	12	10	8
Intellectual disturbances	8	6	2	2	0	0
'Psychopathies'	4	3	0	0	0	0
ot institutionalized or been stitutionalized						
Intellectual disturbances	157	58	23	15	15	8
'Psychopathies'	48	32	12	11	6	6
Other nervous disorders	231	75	48	33	35	21
Total	490	93	101	49	66	31

It is very well possible, therefore, that the constitutional disposition presupposed by us is partly expressed in a higher incidence of peripheral neurological disturbances.

Psychiatric disturbances

Psychiatric disorders were divided into two groups, distinguished on the basis of whether or not they had led to institutionalization. Apart from personal observations, hetero-anamnesis and information obtained from the medical authorities in charge were used to ensure as comprehensive a picture as possible.

A survey of the incidence of psychiatric disorders is presented in Table 5 (p. 93)

In both groups, the number of cases of schizophrenia and manic-depressive psychosis is small (and within the same limits). There are more marked differences in psychotic conditions under another diagnosis. In this respect the encephalitis group included more tainted families than the control group. The number of intellectual disturbances necessitating institutionalization was also larger in the encephalitis group.

An even more marked difference is seen in the category of intellectual disturbances not necessitating institutionalization. The standard used in this group was the repetition of two or more classes at elementary school.

In 58 out of 107 encephalitis families there was a total of 1[illegible] positive findings, as against a total of 23 in 15 out of 102 control families. Similar figures were found with regard to the psychopathic reaction pattern.

The category of 'other nervous disorders' includes such psychiatric conditions as could not be classified under any of the above diagnostic headings. The relations in this group were similar to those in the group of intellectual disorders.

Since there was a relatively large number of psychiatric anomalies, a subdivision was made according to the incidence of the various affections, classified according to family size.

The predominance expressed in the overall results of institutionalized patients (Table 6) is less apparent when the families are compared according to family size.

TABLE 6 INSTITUTIONALIZED PATIENTS

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	1	*50*	2	17	3	13	6	30	10	30	8	47	30	28
Control group	1	*33*	2	10	7	18	3	12	4	40	0	*0*	17	17
Own control group	1	*33*	2	14	4	21	1	*11*	2	*33*	0	*0*	10	19

TABLE 7 INTELLECTUAL DISTURBANCES

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	*0*	3	25	9	39	12	60	21	64	13	76	58	54
Control group	0	*0*	0	0	9	23	4	15	1	10	1	33	15	15
Own control group	0	*0*	0	0	5	26	2	*22*	0	*0*	1	*100*	8	15

TABLE 8 PSYCHOPATHY

	10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	*0*	2	17	9	39	6	30	10	30	5	29	32	30
Control group	0	*0*	2	10	2	5	5	19	2	20	0	*0*	11	11
Own control group	0	*0*	2	14	1	5	2	*22*	1	*17*	0	*0*	6	12

TABLE 9 OTHER NERVOUS DISORDERS

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	*0*	8	67	19	83	13	65	24	73	11	65	75	70
Control group	2	*67*	6	30	12	30	7	27	5	50	1	*33*	33	32
Own control group	2	*67*	6	43	5	26	4	*44*	4	*67*	0	*0*	21	40

TABLE 10 PSYCHIATRIC DISTURBANCES

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	1	*50*	9	75	21	91	16	80	30	91	16	94	93	87
Control group	3	*100*	11	55	18	45	11	42	9	90	2	*67*	51	50
Own control group	3	*100*	11	79	8	42	4	*44*	5	*83*	1	*100*	32	62

TABLE 11 EPILEPSY

	Convulsive states in infants	Grand mal epilepsy	Other forms of epilepsy	Total number of epileptic manifestations	Number of families
Encephalitis group	61	21	5	87	43
Control group	14	10	1	25	21
Own control group	3	2	1	6	6

Whenever the percentage of tainted families in the encephalitis group exceeded that in the control group, the difference was more marked than in the reverse case.

Few other conclusions can be derived from this variable aspect of the findings obtained.

The marked difference between the various groups in the different columns of Table 7, in addition to the marked difference in overall results, warrants the conclusion that the encephalitis group is more heavily tainted with feeblemindedness than the control group

A similar conclusion applies to the group of psychopathic anomalies (Table 8) Although the differences are less striking, the constancy of the deviation in each column would seem to support our view that the number of families in which psychopathic reaction patterns occur is larger in the encephalitis group than in the control group

As could be expected from Table 5, the percentages given in Table 9 (with the exception of a small group of families of less than 10 members) reveal a heavier taint in the encephalitis group

Table 10 presents a survey of families with one or several psychiatric disorders, regardless of further diagnosis and again taking family size into account.

A survey of the various data shows that the picture of the various psychiatric disturbances supports the hypothesis that the neuropathic constitution supposed by us is partly manifested by the increased incidence of labile psychological structures

Epilepsy

A survey of Table 11 immediately reveals that the number of manifestations in each of the groups separately is larger in the encephalitis group than in the control group

The number of families in which epileptic manifestations were recorded proved to be about twice as large as that in the control group The distribution over the groups according to family size is shown in Table 12.

This survey likewise shows a heavier taint in the encephalitis group. For grand mal, the figures reproduced in Table 13 were found

With the exception of the 2nd and 6th column, the percentages of

TABLE 12 EPILEPTIC MANIFESTATIONS

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	0	1	8	8	35	9	45	17	51	8	47	43	40
Control group	0	0	2	10	10	25	5	19	2	20	2	67	21	20
Own control group	0	0	1	7	3	16	0	0	1	17	1	100	6	12

TABLE 13 GRAND MAL EPILEPSY

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	0	0	0	3	13	4	20	3	9	5	29	15	13
Control group	0	0	1	5	4	10	1	4	0	0	2	67	8	8
Own control group	0	0	0	0	1	5	0	0	0	0	1	100	2	4

TABLE 14 CONVULSIVE STATES IN INFANTS

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	0	1	8	6	26	6	30	14	42	5	29	32	30
Control group	0	0	1	5	7	18	4	15	1	10	0	0	13	13
Own control group	0	0	1	7	2	11	0	0	0	0	0	0	3	6

the encephalitis group are higher. This tendency is even more marked in the data on convulsions in infants (Table 14).

In view of the considerable difference between the encephalitis group and the control group in the number of tainted families, and also on the basis of the instructive proportions of the various manifestations in the different groups, it can be considered highly probable that the epileptic taint in the encephalitis group exceeds that in the control group.

Migraine

The data on incidence provide an equivocal picture In the encephalitis group 17 cases of migraine occurred in 9 families In the control group these figures were 17 in 13 families, in our own control group 5 in 4 families

On the basis of these data, no definite conclusion can be reached at this time as to any taint, in any direction

Status dysraphicus

The stigmata of status dysraphicus can be divided into three groups, viz

(1) Chief anamnestic characteristics These are characteristics which can be verified with sufficient certainty from the anamnesis

(2) Chief characteristics observed. In this category the anamnestic data were not sufficiently reliable, so that only personal observations were taken into account

(3) Additional characteristics These were recorded as absent or present only after personal observation

In groups 2 and 3, characteristics were classified as unknown when only anamnestic data on the probands were available The following characteristics were found

Chief anamnestic characteristics:

Anencephalia
Hydrocephalus
Spina bifida aperta
Kyphoscoliosis with unmistakable humpback
Enuresis nocturna over the age of 10

Chief characteristics observed:

Marked or unmistakable unilateral or bilateral pes cavus
Kyphoscoliosis but not with unmistakable humpback
Irregular build of vertebral column
Vertebral column without the normal kyphosis-lordosis structure
Funnel chest
Neurological changes attributable to myelodysplasia.

Additional characteristics:

Mild unilateral or bilateral pes cavus
Depressed sternum
Pigeon chest
Enuresis nocturna over the age of 5
Unilateral or bilateral curvature of the little finger
Acrocyanosis
Ogival palate
Gnatho-palato-cheiloschisis
Stigmata of arachnodactylia.

In the following, the other dysraphic stigmata are disregarded i
order to facilitate systematic elaboration. The following combination
were encountered.

	Chief anamnestic characteristics	*Chief characteristics observed*	*Additional characteristic*
Definitely dysraphic (+)	present	present	present
	present	present	absent
	present	absent	present
	present	unknown	present
	absent	present	present
Dubiously dysraphic (;)	present	absent	absent
	present	absent	unknown
	absent	present	absent
	absent	present	unknown
	absent	absent	present
	absent	unknown	present
Dubiously negative ( )	absent	unknown	unknown
Negative (—)	absent	absent	absent

TABLE 15 GRADES OF DYSRAPHISM

	Definitely dysraphic +	*Dubiously dysraphic* ±	*Dubiously negative* ∓	*Negative* —	*Total number of persons*
Encephalitis group	596	583	1036	269	2484
Control group	103	409	711	621	1866
Own control group	63	211	346	275	895
Control group Van der Wiel	40	198	375	358	971

TABLE 16 GRADES OF DYSRAPHISM IN PERSONS OVER 20 YEARS OF AGE

	Definitely dysraphic +	*Dubiously dysraphic* ±	*Dubiously negative* ∓	*Negative* —	*Total number of persons*
ncephalitis group	476	456	770	193	1895
ontrol group	94	351	563	537	1545
wn control group	57	174	271	219	721
ontrol group Van der Wiel	37	177	292	318	824

Using the above classification, we found the figures given in Table 15 in the various groups.

Since a number of dysraphic stigmata become more marked as the individual approaches adult proportions, Table 16 gives a survey of the dysraphic taint in subjects over 20 years of age.

The reliability of the data collected increases when the probands can be personally examined. The anamnestic data, however well collected and regardless of the good cooperation of test subjects, have again and again shown a variety of gaps.

A good understanding of the proportions in terms of dysraphic taint, therefore, can be obtained by considering the results of the investigation in subjects completely or partially examined. Table 17 gives a survey of the results obtained in this manner. The data have been subdivided according to the generation. In the second part of Table 17, a division is given according to the geographic distribution of the test subjects so as to give an impression of possible local factors.

Although the interpretation of the proportions of the figures given here may be subject to some justified criticism, these figures nevertheless give the impression that the percentage of positive dysraphics among the number of examined subjects in Tilburg exceeds that in the other two geographic groups, whereas the percentages in each of these groups in turn exceed that in the control group.

If the encephalitis group has a heavier dysraphic taint, then this should be reflected in the occurrence of fatal dysraphia. Of course no fatal dysraphia occurs in the A-generation. In the B-generation of the encephalitis group there are 1,449 subjects, including 213 parents. The number of subjects in this generation who may develop a fatal dysraphic affection, therefore, is 1,236. Three instances of fatal dysraphia were recorded in this group. The C-generation of the same group consists of 611 subjects, including 109 patients with post-vaccinial encephalitis. Among the 502 subjects who could have manifested fatal dysraphia, 4 did develop this condition.

In our own control group there were 454 possible subjects in the B-generation No case of fatal dysraphia was reported, and the same holds true for the C-generation (129 subjects) Corresponding figures in the Van der Wiel control group were 426 and 195, without a case of fatal dysraphia The Central Bureau of Statistics in the Netherlands,

... DYSRAPHISM OF EXAMINED PERSONS

Generation	Group	Number of totally examined persons: Number of persons	Dysraphism +	Dysraphism ±	Dysraphism ∓	Dysraphism —	Number of partially examined persons: Number of persons	Dysraphism +	Dysraphism ±	Dysraphism ∓	Dysraphism —
A	Encephalitis	79	24	28	—	27	21	—	6	15	—
	Controls	119(84) [1]	5(4)	26(22)	—	81(54)	8(8)	—	1(1)	7(7)	—
B	Encephalitis	820	360	317	—	143	86	2	42	42	—
	Controls	677(335)	71(45)	246(134)	—	360(156)	13(13)	—	4(4)	9(9)	—
C	Encephalitis	438	209	150	—	79	32	—	11	21	—
	Controls	336(122)	27(14)	121(45)	—	188(63)	—	—	—	—	—
A	Tilburg	8	1	5	—	2	1	—	—	1	—
B		214	120	74	—	20	8	—	3	5	—
C		94	78	13	—	3	—	—	—	—	—
A	Remaining parts of Brabant	11	3	4	—	4	2	—	—	2	—
B		164	62	72	—	30	5	—	3	2	—
C		110	55	36	—	19	—	—	—	—	—
A	Rest of the Netherlands	60	20	19	—	21	18	—	6	12	—
B		442	178	171	—	93	73	2	36	35	—
C		234	76	101	—	57	32	—	11	21	—

[1] The number in parentheses refers to our own ...

reporting on the period 1951 through 1957, recorded about 800 instances of fatal dysraphia in the groups of stillbirths and deaths, at an annual birth rate of about 230,000, *i.e.* about 1 in 300 births.

Comparing the records of our groups under investigation with the above figures, we find a frequency of about 1 in 400 births in the B-generation of the encephalitis group, and about *1 in 125 births* in the C-generation. The last-mentioned rate would seem to indicate a heavier dysraphic taint.

The difference between the B-generation and the C-generation is probably partly based on the fact that the average age in the B-generation is higher, so that data on perinatal mortality are less reliable in this category. The fact that, in tracing cases of fatal dysraphia, ignorance and positive concealment are of great importance, is rather obvious.

The figures presented, therefore, are likely to be lower than the actual values.

The following measures were taken to ensure that the dysraphic taint in the various groups should be approached with optimal mathematical reliability *.

We calculated the frequency of occurrence of 'certain dysraphia' (definitely positive), 'probable dysraphia' (dubiously positive), 'definitely no dysraphia' (negative) and the remaining group of 'probably no dysraphia' (dubiously negative). The average frequency of each of the four grades of dysraphism per group, per generation, can be calculated in two ways, *viz.* by calculating the frequency for all subjects per group, and by averaging the above-mentioned frequencies.

Since the grade of dysraphism per family may differ, and since on the other hand the grade of dysraphism may depend on the family size, we believe that the second method (averaging the frequencies) is to be preferred. In this manner, the average frequencies indicated in Table 18 (p. 107) were obtained.

This table furnishes the following information:

(1) In the A-generation, the dubiously negative and the negative

* The mathematical elaboration was carried out by the Department of Elaboration of Results Observed, of the Central Organization for Applied Physical Research T N O).

cases in the two control groups were diagnosed to different degrees. (2) In the B-generation, the negative cases in the two control groups were diagnosed to different degrees. If the frequencies per family could be regarded as independent, normally distributed variables, then these differences would be significant at the 5% level.

It is an obvious supposition that this difference between the two control groups may be correlated either with the choice of material or with differences in diagnosis or interpretation of the changes. Once more this demonstrates the necessity of prudence in dealing with 'objective' figures in medicine.

In view of this it would seem to be advisable, for the time being, to compare the encephalitis group exclusively with our own control group, using the Van der Wiel control group only for illustration. Such a comparison leads to the following conclusions:

(1) In the A-generation there is only an indication that the dysraphism in the encephalitis group exceeds that in our own control group; the Van der Wiel group points in the same direction

(2) In the B-generation the result is more unequivocal The definitely dysraphic fraction is significantly larger and the definitely negative fraction significantly smaller in the encephalitis group, the two dubious fractions show about the same frequency in the encephalitis group and in our own control group. The Van der Wiel group shows the differences found with regard to the encephalitis group to a more marked degree.

(3) In the C-generation, the difference between the encephalitis group and our own control group as to the frequency of certain dysraphia is highly significant In negatives, too, the difference is naturally very significant, but in this respect we are confronted with the complication that the dubious negatives predominate in the encephalitis group The data on the C-generation have the disadvantage that this generation is represented by only 1 or 2 subjects in many families, the fractions presented, consequently, are pure estimates of the average dysraphism per family but significance calculations can hardly be made.

For the B-generation, we also calculated a weighed mean of the fractions found, after transformation by the method of angular transformation, which renders variance virtually independent of the

frequency. Bartlett's correction was applied, replacing fractions of 0% and 100%, respectively, in a family of n persons by $(100/2n)$%, and $100\%-(100/2n)\%$, respectively. This correction ensures further stabilization of the variance and, in our cases, has the additional advantage that the observation of 0% (relatively often made in the control groups, particularly with small family size) does not exert too marked an influence on the mean frequency. Because in angular transformation the variance is inversely proportional to the number of observations, *i.e.* the family size, this size must be used as weight in calculating mean and variance. When this method is applied, therefore, large families exert a more marked influence on the means than the small families.

In the B-generation, this was found not to have an important effect on the mean values (as compared with the method discussed earlier) The average percentages in Table 19 shown were obtained by re-calculation from the angles

Owing to the transformation, the total of re-calculated percentages is no longer exactly 100%. Again, the differences between the encephalitis group and the two control groups in dubiously positive and negative results are only small; the difference in *definitely positive and* definitely negative results are very marked and highly significant

The method employed also makes it possible to verify whether the grade of dysraphism differs from family to family. If this is not the case, then the variance of transformed percentages—after weighing with the aid of family size—should theoretically be $90^2/\pi^2 = 820.7$. We found the values of Table 20 for these variances.

This table shows that, in both control groups, the variances of the definitely positive and dubiously positive results do not significantly differ from the theoretical variance. The variances of the negative results, however, do differ significantly from the theoretical variance. A plausible explanation of this fact may in our opinion be found in the fact that the separation between negatives and dubious negatives has not been made in the correct place and that, in fact, the dysraphism in each of the two control groups has a frequency which is the same for the majority of the families.

The encephalitis group shows an entirely different picture; the variance found here is invariably highly significantly larger than the

TABLE 18 DYSRAPHISM IN PERCENTAGES

	Definitely positive	Dubiously positive	Dubiously negative	Negative
A-generation				
Encephalitis group	6 5	10 3	83.5	6 8
Own control group	1 9	13 0	59.1	26 0
Van der Wiel group	0 5	4 0	82.0	13 5
B-generation				
Encephalitis group	25 4	25.1	39 6	9 9
Own control group	8 7	26 7	35 9	28 7
Van der Wiel group	5 1	22 4	33 5	39 0
C-generation				
Encephalitis group	31 0	30 3	25 8	12 9
Own control group	10 1	32.5	5 6	51 8
Van der Wiel group	4 9	33 8	9 9	51 5

TABLE 19 DYSRAPHISM (AVERAGE PERCENTAGES)

	Definitely positive	Dubiously positive	Dubiously negative	Negative
B-generation				
Encephalitis group	23 8	24 5	83 4	9 8
Own control group	9 1	23 7	38 5	26 8
Van der Wiel group	7 3	20 7	33 5	38 0

TABLE 20 DYSRAPHISM (VARIANCES OF TRANSFORMED PERCENTAGES)

	Definitely positive	Dubiously positive	Dubiously negative	Negative
B-generation				
Encephalitis group	1979 7	1158 5	2641 6	1028 2
Own control group	615 8	966 2	1130 1	1344 0
Van der Wiel group	305 5	799 5	2551 7	1509 5

theoretical variance. This may indicate that the dysraphic taint in the encephalitis group differs in the various families.

The fact that the most unmistakable picture is found precisely in the B-generation need not surprise us. After all, this is the generation which includes few infants, so that diagnosis of the changes is much less difficult than in the C-generation. Apart from this, a larger percentage of the B-generation than of the A-generation could be examined, as the loss due to death in the latter generation is higher.

An overall consideration of these data warrants the conclusion that the dysraphism in the encephalitis group significantly exceeds that in the control group.

Allergic disorders

The possibility that post-vaccinial encephalitis might be an allergic reaction of the CNS has been previously discussed in some detail

While data on other allergic affections are of interest to us, if merely from the point of view of the problem of neuropathic constitution, they are even more interesting in view of the question of a possible correlation between affections known to be allergic and so-called neuro-allergy.

Our investigation was limited to the most widely known syndromes of which Table 21 gives a survey.

This table shows that the number of families in which allergic disorders occur is larger in the encephalitis group than in the control group, for all affections except hay fever.

The number of families in which any allergic affection occurs is also larger in the encephalitis group, as is shown in *Table 22.*

In accordance with family size, expressed in percentages, we found the distribution of tainted families for infantile eczema as reproduced in Table 23.

Whenever percentages in the control group are higher than those in the encephalitis group, the figures are printed in italics. The more reliable percentages point in the direction of a heavier taint in the encephalitis group

There were even more marked differences in the families tainted with bronchial asthma (Table 24) With the exception of the second

(text cont'd p. 113)

TABLE 21 ALLERGIC DISORDERS

Group	Eczema infantum		Bronchial asthma		Hay fever		Urticaria		Others		Total number of	
	Number	Number of families	Number	Number of families	Number	Number of families	Number	Number of families	Number	Number of families	Cases	Families
Encephalitis	29	23	38	27	4	4	18	14	4	4	2484	107
Controls	12	9	20	19	13	10	5	3	1	1	1866	102
Own controls	10	7	6	6	6	5	3	1	0	0	895	52

TABLE 22 NUMBER OF FAMILIES WITH ONE OR MORE ALLERGIC STIGMATA

Group	+	−	Total number of families
Encephalitis	53	54	107
Controls	32	70	102
Own controls	15	37	52

TABLE 23 ECZEMA INFANTUM

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	1	50	2	17	5	22	4	20	8	24	3	18	23	21
Control group	0	0	2	10	2	5	3	12	1	10	1	33	9	9
Own control group	0	0	2	14	0	0	3	33	1	17	1	100	7	13

TABLE 24 BRONCHIAL ASTHMA

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	0	2	17	7	30	7	35	7	21	4	23	27	25
Control group	0	0	5	25	9	23	4	15	1	10	0	0	19	19
Own control group	0	0	3	21	1	5	1	11	1	17	0	0	6	12

TABLE 25 HAY FEVER

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	0	1	8	1	4	0	0	2	6	0	0	4	4
Control group	0	0	4	20	2	5	3	12	1	10	0	0	10	10
Own control group	0	0	3	21	0	0	1	11	1	17	0	0	5	10

TABLE 26 URTICARIA

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	0	3	25	3	13	2	10	5	15	1	6	14	13
Control group	0	0	2	10	0	0	0	0	1	10	0	0	3	3
Own control group	0	0	0	0	0	0	0	0	1	17	0	0	1	2

TABLE 27 ENDOCRINE-DIENCEPHALIC STIGMATA

Group	Goitre		Diabetes mellitus		Obesity		Others	
	Number of cases	Number of families	Number of cases	Number of families	Number of cases	Number of families	Number of cases	Number of families
I	53	25	36	26	164	65	73	42
II	13	9	29	25	62	40	24	22
III	11	7	12	11	38	24	15	13

Group I· Encephalitis group
Group II Control group.
Group III. Own control group.

according to family size and expressed in percentages, the data on the occurrence of one or several endocrine-diencephalic disorders in the family are shown in Table 29.

Apart from the first column, the percentages in the encephalitis group are higher than those in the control group. Comparison with our own control group, however, yields less convincing results

Table 30 presents a survey of the number of families in which one or several cases of goitre occurred, also divided according to family size.

All percentages are higher in the encephalitis group than in the control group, with the exception of the first and fifth column.

As could be expected from the above survey, the distribution of families tainted with diabetes mellitus, according to family size, revealed so small a difference between the two groups that a heavier taint in the encephalitis group cannot be suggested (Table 31)

The data on obesity—so suggestive in the general survey—lose convincing power in view of the figures reproduced in Table 32.

Although there are again some arguments in favour of a heavier tainting of the encephalitis group, reversed proportions are also seen (particularly in the third column).

The findings in the area of 'other endocrine-diencephalic disorders' are reproduced in Table 33 In this table, we find no positive findings in the first two columns in the encephalitis group. Yet the other findings, as in the case of obesity, support the suggestion that these stigmata are more frequent in the encephalitis group.

Skin malformations

Anomalies in the skin pigmentation were recorded as: (a) café-au-lait spot, (b) naevus pigmentosus and (c) depigmentation.

Table 34 shows that the frequency of pigmental anomalies in the encephalitis group is about the same as that in the control group

The number of families in which these stigmata were found is also about the same in both groups

A heavier taint of the encephalitis group in this respect was not demonstrable.

Haemangiomata were slightly more frequent in the encephalitis group The number of families in which haemangiomata were found is about twice as large in the encephalitis group (Table 35).

TABLE 29 ENDOCRINE-DIENCEPHALIC STIGMATA

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	1	*50*	8	67	17	74	17	85	32	97	15	88	90	84
Control group	3	*100*	10	50	26	65	16	62	7	70	2	67	64	63
Own control group	3	*100*	17	50	14	74	8	*89*	5	*83*	1	*100*	38	73

TABLE 30 GOITRE

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	*0*	1	8	4	17	6	30	6	18	8	47	25	23
Control group	1	*33*	1	5	1	3	3	12	2	20	1	*33*	9	9
Own control group	1	*33*	1	7	0	0	3	*33*	2	*33*	0	*0*	7	13

TABLE 31 DIABETES MELLITUS

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	*0*	2	17	3	13	7	35	8	24	6	35	26	24
Control group	0	*0*	4	20	10	25	7	27	4	40	0	*0*	25	25
Own control group	0	*0*	1	7	5	26	3	*33*	2	*33*	0	*0*	11	21

TABLE 32 OBESITY

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	1	*50*	5	42	7	30	15	75	27	82	11	65	66	62
Control group	2	*67*	5	25	17	43	9	35	5	50	2	*67*	40	39
Own control group	2	*67*	4	29	9	47	5	*56*	3	*50*	1	*100*	24	46

TABLE 33 OTHER ENDOCRINE STIGMATA

	< 10		10 up to 14		15 up to 19		20 up to 24		25 up to 29		≥ 30		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Encephalitis group	0	*0*	0	0	7	30	8	40	16	48	11	65	42	39
Control group	1	*33*	4	20	10	25	4	15	2	20	1	*33*	22	22
Own control group	1	*33*	3	21	7	37	1	*11*	0	*0*	1	*100*	13	25

TABLE 34 ANOMALIES OF PIGMENTATION

	−	+	Number of families	Café-au-lait spot	Naevus Pigmentosus	Depigmentation
Encephalitis group	1244	92	58	67	21	4
Control group	1040	92	61	82	8	1
Own control group	500	41	29	33	7	1

TABLE 35 HAEMANGIOMATA

	Present	Absent	Number of families
Encephalitis group	16	1320	14
Control group	9	1123	8
Own control group	3	538	3

TABLE 36 OTHER SKIN DISORDERS

	Present	Absent	Number of families
Encephalitis group	57	1279	35
Control group	28	1104	21
Own control group	21	520	15

TABLE 37 OTHER SKIN DISORDERS

	Lipomata		Fibromata		Psoriasis		Ichthyosis		Others	
	Number	Number of families	Number	Number of families	Number	Number of families	Number	Number of families	Number	Number of families
Encephalitis group	7	7	14	12	12	10	18	6	6	6
Control group	0	0	5	4	11	7	2	2	10	10
Own control group	0	0	5	4	8	5	2	2	6	6

TABLE 38 INTERNAL DISORDERS DURING LIFE

	Tuberculosis	Number of families	Carcinoma	Number of families	Acute Rheumatism	Number of families	Chronic Rheumatoid Arthritis	Number of families	M. Bechterew	Number of families	Vitium cordis	Number of families	Congenital disorders	Number of probands
Encephalitis group	42	34	4	4	8	8	23	20	1	1	68	47	—	1770
Own controls	13	13	6	6	1	1	4	3	2	2	12	11	—	688
Controls Van der Wiel	2	2	3	3	—	—	8	6	—	—	4	4	1	612
Total number of controls	15	15	9	9	1	1	12	9	2	2	16	15	1	1300

A division of haemangioma frequency according to family size is impossible in view of the small number of families. This would not give a better understanding The figures given point in the direction of a heavier taint in the encephalitis group

In the survey of other skin changes there were more changes in the encephalitis group (Table 36) Since these phenomena, when divided according to nature, provide a heterogeneous picture, we considered it advisable to present a survey of the skin anomalies included in this group in Table 37

In this respect it can be pointed out that the number of lipomata in the encephalitis group exceeds that in the control group The difference is less obvious for the fibromata. There is indeed a difference between the encephalitis group and the control group, but the figures for our own control group render this difference dubious The incidence of psoriasis shows no marked difference between the two groups

The occurrence of ichthyosis may be more significant; 18 cases of this condition were registered in 6 families of the encephalitis group

Although these data do not warrant any definite conclusions it can be pointed out that whenever a difference occurred in these groups of skin changes, this difference was invariably in favour of the encephalitis group

Disorders in the field of internal medicine

In Table 38 a survey is presented of registered changes in the field of internal medicine, as found in the various groups during life

The number of families with tuberculosis in the encephalitis group exceeds that in the control group In view of the data on causes of death, this fact is supported only by the proportions of the tuberculosis figures in the B-generation Yet the figures found are rather strongly suggestive of an increased susceptibility to tuberculosis

Nothing can be said of the incidence of carcinomata, particularly if we include the carcinomata recorded as cause of death In the field of rheumatic conditions there are higher frequencies in the encephalitis group again

A remarkable feature is the marked difference in the number of families having one or several cases of organic heart defect

Concomitance of congenital cardiopathies and dysraphic stigmata has been discussed in detail by such investigators as Bijl, who raises the question of a possible predisposition to cardiac affections in general. The data of this table, and the heavier dysraphic taint in the encephalitis group, might tend to confirm this possibility.

Other degenerative stigmata

Apart from the above-mentioned changes, such stigmata as could probably be largely attributed to dysontogenesis were also registered; they are generally indicated as 'degenerative' stigmata

A number of these stigmata listed below are closely related with the status dysraphicus Their occurrence probably depends on a dysraphic condition although, in genetic terms, they are more independent than the dysraphic stigmata listed earlier. The exact nature of these relationships is still obscure. As long as this is the case, it would seem to be advisable to keep these stigmata separated.

A survey follows of the anomalies found:

ENCEPHALITIS GROUP

Cranium

Oxycephalia	1
Bathrocephalia	1
Mandibulofacial dysostosis	3 in 1 fam.
Hypertelorism	4 in 4 fam.
Reduced interocular distance	1
Internal frontal hyperostosis	1
Prognathism	5 in 4 fam.
Mandibular hypoplasia	3 in 3 fam.

Eyes

Nystagmus to left and right	14 in 11 fam
Strabismus	35 in 25 fam.
Marked myopia	7 in 6 fam.
Congenital ptosis bilateral	6 in 3 fam
unilateral	5 in 2 fam

Blepharophimosis	5 in 4 fam.
Congenital bilateral loss of abductor function	1
Simple heterochromia of the iris	12 in 6 fam.
Early cataract	2 in 1 fam
Congenital blindness	1
One amblyopic eye	1

Ears:

Malformation of the external ear	2 in 2 fam
Congenital deafness	1
Deafness	15 in 7 fam

Extremities:

Brachydactylia	11 in 4 fam.
Syndactylia	11 in 9 fam
Other radial anomalies	3 in 3 fam
Excessive flaccidity (Hyperlaxité)	16 in 10 fam
Congenital luxation of the hip	3 in 3 fam
Dupuytren's contracture	3 in 3 fam.

Other stigmata:

Abortive form of achondroplasia	5 in 4 fam.
Anal atresia	1
Hyperthelia	2 in 2 fam.
Total number of anomalies	181 in 68 fam

OWN CONTROL GROUP

Cranium

Prognathism	1
Mandibular hypoplasia	1

Eyes

Nystagmus to both sides	3 in 3 fam
Strabismus	10 in 8 fam
Marked myopia	6 in 4 fam.
Marked hypermetropia	1
Early cataract	1
Simple heterochromia of the iris	3 in 3 fam
Unilateral ptosis	1
Congenital unilateral abductor paresis	1

Ears

Deafness	2

different vaccines gave rise to varying numbers of cases of vaccinia generalisata. This was not the case with post-vaccinial encephalitis. This would tend to support the theory of there being no (or at least no positive) correlation between the dermal and cerebral phenomena. An objection to one scar will be that the number of failures to 'take' in young children will probably increase. Doorschodt has shown that the number of pock marks is smaller in the case of children whose mothers had been vaccinated a short time previously than in those whose mothers had been vaccinated many years previously, or not at all. *She further stated that there was a correlation between the immunity* and the number of pockmarks (see page 127). Nevertheless, one pockmark would conform to the requirements of the law, which is an argument stressed by Sillevis Smitt.

The fact that a new vaccinostyle should be used for each new vaccination is obvious. English workers have suggested intra- or even sub-cutaneous vaccination (Stuart). It has yet to be proved that this will improve the prognosis.

Paschen believes that the reduction of the skin reactions brings with it no certainty of a reduction in encephalitides. This may also be the explanation of the fact that dilution of the vaccine also has no effect on encephalitis (David). Next, we must consider the question of whether the nature of the vaccine itself has anything to do with the development of post-vaccinial encephalitis. In doing this, we omit all mention of the many theories concerned with the etiology of encephalitis postvaccinialis, but refer the reader to the appropriate chapter. This is not to deny that there is a connection between the two problems.

It is obvious that as long as the 'activating theory' is not completely discarded it is wise not to vaccinate at times when virus infections are prevalent. Further, the number of micro-organisms found as impurities in the vaccine must of course be kept as low as possible. These, however, do not concern us; we are interested in the vaccine '*an sich*'. We are now forced to fall back on empiricism. The Encephalitis Report of 1932 denies any connection between the development of post-vaccinial encephalitis and the sort of vaccine used. More recent reports also deny any positive correlation between the two. The choice of vaccine therefore probably does not play a rôle, but it seems wise to continue to collect statistics concerning this matter. Perhaps as

analysis covering a long period of time may be able to lead to a definitive answer.

Frenkel and Kapsenberg have occupied themselves with the production of contamination-poor and -free vaccine. Ordinary vaccine, produced by culture on calves, has several disadvantages The bacterial impurities are reduced by the addition of glycerol and by storing at −10 to −20° C for two years (in the Netherlands) This time-consuming method of production can lead to difficulties, for example during times of increased demand In addition to which, the vaccine must be used within one week of delivery, and standardization of the product is not possible. Three methods for the production of a bacteria-free vaccine have been mentioned: (a) neurovaccine (Gallard, Levaditi and Nicolau), (b) egg-passage and (c) culture.

In this last method, Kapsenberg uses the epidermis of cow tongue. The vaccine produced proved to have the same immunizing powers in calves as the ordinary vaccine Serum from cows immunized with Amsterdam virus neutralizes the cultured virus It is also possible to filtrate the material; the optimal titer is probably in the neighbourhood of 10^{-6} to 10^{-7}. This vaccine is difficult to use, however It is watery and therefore adheres poorly to the skin Its immunizing powers in human beings have yet to be determined When it becomes available for large-scale use we shall be able to see whether it offers a possibility of reducing post-vaccinial neurological complications.

Nelis proposed using a vaccine prepared with a solution of formol This should diminish the encephalitogenic factors, without influencing the immunization against smallpox

The 1954 regulations concerning vaccination of military personnel are as follows The vaccine used must come from an accredited vaccine centre The instruments used for the vaccination must be sterile. A sterilized or new sterile vaccinostyle or needle is to be used for each person being vaccinated The vaccine may be allowed to come into contact only with clean, sterile objects. Thus an object that has been in contact with skin or blood may never be held or dipped into the vaccine (danger of serum hepatitis) Continuous control is necessary for the development of an immaculate technique. This technique will consist of either the multiple pressure method or the scratch method, and in both cases there must be an absolute minimum

of bleeding. The surface used in the former method *must not be greater* than 0.5 cm², with a diameter of 8 mm. In using the scratch *method*, 2 scratches are to be made of 0.5 cm long, at at least 2 *cm distance* from one another. The vaccination site must be *cleaned with either ether or soap and water. After* vaccination, the excess of vaccine must be *allowed* to dry in place, removed with a clean piece of cotton, or covered with a clean gauze-pad. It is advisable to keep the vaccination site dry.

In addition to all these measures concerning the vaccine, an attempt has been made to decrease the number of cases of post-vaccinal encephalitis by means of various chemical-humeral procedures. We shall merely mention the abstinence from eating *meat following* vaccination A rational basis for this has *never been demonstrated.* Drogendijk has advocated the use of Pernaemon as a prophylactic He has not seen any encephalitis following vaccination combined with administration of Pernaemon.

Many authors (Melville MacKenzie, Fyfe, Flemming and others) have reported the favourable results of the use of *immune serum* It is believed that the anti-bodies here combat the vaccine virus or some other (encephalitogene) virus, one of these being the cause of post-vaccinial encephalitis. In The Netherlands attempts are also being made to gain more certainty about the use of *immune serum. It is probable that* gamma globulin and hyperimmune gamma globulin are even more effective. The skin reaction to the vaccination is not affected. (This, however, is not very significant. See the above concerning the correlation between dermal and cerebral reactions)

The following report by Trostdorf of a case of varicella encephalitis gives us food for thought (at least if we accept the existence of parallel mechanisms) He describes a girl of 3½ years of age who was exposed to intermittent cold over a period of several months. During this period she suffered from transient attacks of squint. She contracted varicella, which was followed by an acute, transient blindness Twelve days after the onset of the chickenpox, she exhibited a slight inequality of reflexes Following the administration of reconvalescent serum, the child developed an acute tetraplegia, which Trostdorf considers as supporting the theory of the allergic actiology of the para-infectious encephalitides The author has no experience in these

matters We have been unable to find descriptions of similar cases in the literature, but it seems reasonable to bear this possibility in mind

(3) *The choice of therapeutic agent (or agents) in cases of encephalomyelitis post-vaccinialis*

The therapy of this disease must, in view of the meagreness of our knowledge concerning the aetiology, at least partly be symptomatic (Govaerts) The part of the therapy that may be called 'specific' varies like the opinion of the physician concerning the aetiology We should now like to mention some of these 'specific' therapies Under prophylaxis we mentioned the use of immune serum This is also used in established cases Van Bouwdijk Bastiaanse was the first to recommend the use of serum from highly-immunized animals At the time no favourable effects were seen. Hekman treated his cases with the intravenous injection of serum from patients who had been very recently vaccinated. He reported satisfactory results Others (Gordon, Paschen, Kokken and others) reported a similar success In the *Bulletin de l'Organisation mondiale de la Santé*, 1947-'43, this serum therapy is mentioned. Verlinde pointed out in his dissertation the possibility that disturbances in hepatic functions may play a rôle in the development of encephalitis. Guanidine may be the most important factor involved here. This is the origin of the Pernaemon-therapy. Kramer has declared that he sees possibilities in this theory and therapy. Statistics concerning this therapy are not yet available so that it is impossible to judge its value.

Using the allergic genesis of post-vaccinial encephalitis as a starting-point, Ligterink believes that he has seen good results following the use of ACTH. Stenczel advises administering calcium. Hyman goes still further and recommends the use of anti-histamines (Some Americans advise using these in the treatment of sclerosis multiplex)

In all of these therapies we can see ill-concealed hypotheses concerning the aetiology. The number of patients is too small to be able to give each of these methods an adequate therapeutic trial, or to derive a reliable opinion based on facts. We are thus forced, in treating cases of post-vaccinial encephalitis, to choose from a group of therapeutics whose value has not yet been proved.

A review of the clinical manifestations of post-vaccinial encephalitis is presented in Chapter 4. The heterogeneity of the manifestations is pointed out. With reference to a statement by De Vries—that no typical (demyelinating) microglial encephalitis is seen under the age of two—an attempt is made to elucidate some of the clinical aspects of this difference.

The incubation periods in the cases of post-vaccinial encephalitis notified during the period 1945/1951 were divided into two groups, with the age of two as the borderline. Two aspects were thus clearly revealed, *viz.*:

The average period of incubation was 9 days in the younger group (with a peak at 7 days), and 11.57 days (with a peak at 12–13 days) in the older group The difference between the averages proved to be significant, as was the difference in the distribution of data around the average. In addition it was found, on statistical grounds, that children under two years of age also show a correlation between the time of vaccination and the subsequent cerebral features. In our opinion, both the pathological-anatomical findings and the above-mentioned clinical data warrant the conclusion that post-vaccinial encephalitis in young children is a clinical entity which differs from that in older subjects.

Among the 109 cases of post-vaccinial encephalitis studied, there were 23 deaths, 38 subjects showed more or less severe residual symptoms This last-mentioned fact is an argument against the view that there are only two possibilities after post-vaccinial encephalitis, *viz* cure without after-effects or a fatal issue.

The classification of post-vaccinial encephalitis recommended by the above-mentioned Encephalitis Committee seems to have retained practical value This classification is as follows:

(1) Cases which can be interpreted with certainty as post-vaccinial encephalitis

(2) Dubious cases, but most likely to be positive.

(3) Dubious cases which may be either positive or negative.

(4) Cases in which the clinical course can only be identified as post-vaccinial but showing no changes definitely indicative of the condition under discussion

The pathological anatomy (Chapter 5) is described largely on the basis of De Vries's work.

Apart from the typical picture of demyelinating perivenous microglial encephalitis previously described by Van Bouwdijk Bastiaanse there are other pathological anatomical pictures which can be interpreted as post-vaccinial cerebral complications Mention is also made of the pathological aspect of encephalitis following revaccination, among other things

As has been pointed out, De Vries found no microglial encephalitis in children under two years of age. The processes involved in these cases are still obscure. The composition of the cerebral substance may be of importance in this respect (Brante, Edgar).

These problems are closely correlated with the etiology, of which a survey is given in Chapter 6 The following etiological theories have so far been forwarded:

(A) *The theory of superinfection*

(1) Bacterial pollution.
(2) A virus in the vaccine
(3) Toxins.

(B) *The theory of activation.*

Activation of a circulating virus is believed to play a rôle

(C) *The vaccine itself causes the encephalitis*

(1) By the virus itself
(2) By an encephalitogenic intermediary product of the virus
(3) As an allergic reaction to the virus.

It is particularly the last-mentioned possibility which is discussed, in connection with data obtained in experimental neuroallergic encephalitis (Wolf, Kobat, Bezer and many others) The features seen in these cases are reminiscent of those of microglial encephalitis Data from the literature on possible provoking factors in the pathogenesis of post-vaccinial encephalitis are discussed

In Chapter 7, a review is presented of publications in which constitutional factors in the pathogenesis of post-vaccinial encephalitis are taken into account In this respect opinions prove to be very

diverse. Several publications, however, mention occurrence of several cases of post-vaccinial encephalitis in one family or the occurrence of degenerative changes in siblings of patients with post-vaccinial encephalitis.

A description is given of some personal observations from the Utrecht University Neurological Clinic. In 1951, Sillevis Smitt once more emphasized the fact that inflammatory changes in the central nervous system are governed by the conception 'electivity' and that this electivity is correlated with constitutional characteristics. This principle is introduced into the field of post-vaccinial encephalitis. This constitutional approach is further elaborated in Chapter 8.

Some general considerations regarding constitution are followed by a discussion of the conception 'neuropathic constitution'. Mention is made of the work done in this field by Bremer, Curtius and others This line of thought was introduced in the Netherlands by Sillevis Smitt.

A more detailed description is given of the fundamental hypothesis underlying this investigation—that constitutional factors in the sense of neuropathic or degenerative stigmata play a rôle in the pathogenesis of post-vaccinial encephalitis Special reference is made to:

(A) Morphological changes.

(B) Endocrine disorders.

(C) Vegetative dysregulation

(D) Allergic stigmata.

(E) Psychiatric disturbances.

To verify this hypothesis against the facts, an investigation was made in 107 families with a series of 109 diagnosed cases of post-vaccinial encephalitis, the investigation was as comprehensive as possible, covering three generations, viz.:

(A) The grandparents' generation.

(B) The parents' generation

(C) The patient's generation (limited to the immediate family).

The findings obtained were compared with those from a similar investigation covering 102 random families (Chapter 9). The former group is referred to as the encephalitis group, and the latter as the control group The investigation indicated that the families in the encephalitis group showed increased susceptibility to

(1) dysraphic stigmata;
(2) neurological changes;
(3) psychiatric disturbances;
(4) epileptic manifestations;
(5) allergic symptoms;
(6) endocrine-diencephalic stigmata;
(7) some internal anomalies;
(8) a variety of other 'degenerative stigmata'.

The skin changes showed a somewhat irregular pattern, interpretat of which is difficult. Some changes (haemangiomata, lipom ichthyosis) showed an increased incidence in the encephalitis gro

In estimating the risk of a vaccination in terms of post-vacci encephalomyelitis, the constitutional disposition of the subjects to vaccinated should therefore be taken into account Investigation relatives with regard to the above-mentioned stigmata is often necess if a well-founded opinion is to be formed

The possibilities of prophylaxis and treatment of post-vacci encephalitis are discussed once more in Chapter 10, in which fi chapter the following considerations are presented

(1) Selection of subjects to be vaccinated

Age is of great importance in this respect It is advisable to inocul children under the age of one year The principles elaborated in course of our investigation also come under this heading Vaccinat of subjects with organic cerebral changes, shortly after injuries of head, etc, should be discouraged

(2) Technique of vaccination and choice of vaccine

A flawless technique observing all precautions is desirable nature of the vaccine has never been demonstrated to exert an influe in this respect. Administration of γ-globulin simultaneous w vaccination possibly has a favourable effect

(3) The choice of medication in the case of post-vaccinial encephali

Treatment varies according to the therapist's views on the pat genic mechanism The therapeutic results obtained are gener discussed in case reports, so that comparison is exceedingly diffic The majority of therapeutic measures taken are symptomatic.

BIBLIOGRAPHY

ANDRÉ-BALISAUX, G, Incidence familiale et facteurs p… l'encéphalite de la vaccination jennérienne.
Acta neurol. belg, 53 (1953) 438.

BABONNEIX, L., Les encéphalites aiguës infantiles à tend…
Arch. int Neurol, 58 (1939) 25

BAUMANN, C., Encephalitis postvaccinalis
Ned milit. geneesk. T., 7 (1954) 233.

BENDA, C. E., Chronic rheumatic encephalitis.
J nerv ment. Dis, 106 (1947) 84

BENDRAT, I, Differentialdiagnose 'encephalitischer' Krankhe…
Dtsch Gesundh -Wes., 4 (1949) 216.

BERGER, K. und F. PUNTIGAM, Über die Erkrankungshäufigke… ner Altersklassen von Erstimpflingen an postvakzinaler E… *Wien med Wschr*, 104 (1954) 487.

BERGER, W. und K. HANSEN, *Allergie. Ein Lehrbuch in …* Leipzig, 1940.

BICKERS, D. S, Postvaccinal encephalitis with pre-existing foca… seizures. Report of a case.
New Engl J. Med, 246 (1952) 929

BIEMOND, A, *Diagnostiek van hersenziekten* Amsterdam 1946

BIEMOND, A, *Enige beschouwingen over erfelijke organische zenuwziekten* Haarlem, 1947 Inaug address, Univ of Amsterdam

BLEULER, M., Erblichkeit und Erbprognose Schizophrenie, manisch-depressives Irresein, Epilepsie, Durchschnittsbevolkerung
Fortschr. Neurol Psychiat, 11 (1939) 287

BLEULER, M Erblichkeit und Erbprognose
Fortschr Neurol. Psychiat., 13 (1941) 49

BOGAERT, VAN, see VAN BOGAERT.

BOGAERT, H, J. MACKEN et J RADERMECKER, Une encephalopathie infantile a évolution subaiguë d'origine inconnue (coqueluche?) et a issue fatale
Acta neurol. belg., 53 (1953) 156.

GREENFIELD, J. G., Encephalitis and encephalomyelitis in England and Wales during the last decade.
Brain, 73 (1950) 141.

GREENFIELD, J. G., The classification of diffuse demyelinating sclerosis of the brain on the basis of pathogenesis.
Folia psychiat. neerl., 53 (1950) 254.

GREENFIELD, J. G., Maladies spontanées démyélinisantes chez l'homme et chez l'animal.
Acta neurol. belg., 54 (1954) 621.

GUILLEMIN, J., L'encéphalite postvaccinale
Sem. Hôp. Paris, 24 (1948) 1027.

HAAR, H. und O. MEINERTZ, Akute Osteomyelitis nach Pocken- und Typhusschutzimpfung.
Münch. med. Wschr., 96 (1954) 87.

HALPERN, B. N., J. BERTRAND et F. LHERMITTE, L'encéphalomyélite allergique expérimentale.
Presse méd., 58 (1950) 684.

HANSEN, K., Nervensystem und Allergie
in: W. BERGER und K. HANSEN, *Allergie*. Leipzig, 1940, pp. 539-559.

HAUSMANN, E., Drei Fälle von Encephalitis postvaccinalis mit besonderem Verlauf.
Öst. Z. Kinderheilk., 5 (1950) 386.

HEMMES, G. D., Bestrijding van pokken en postvaccinale encephalitis
T. soc. Geneesk., 28 (1950) 5.

HERRLICH, A., W. EHRENGUS and J. WEBER, Untersuchungen über Disposition und Prognose der Encephalitis postvaccinalis.
Münch. med. Wschr., 98 (1956) 156

HESS, W. R., *Die funktionelle Organisation des vegetativen Nervensystems*
Basel, 1948.

HEUCQUEVILLE, D', see D'HEUCQUEVILLE.

[illegible] 'encephalitis'

HOFBAUER, A., Erfahrungen mit der subkutanen Blatternimpfung in der Landpraxis.
Wien. klin. Wschr., 61 (1949) 848.

HORST, VAN DER, see VAN DER HORST.

HOTTLE, G. A., C. A. NEDZAL, J. WRIGHT and F. J. BELL, Allergic encephalitis following injection of dialysate of brain tissue
Proc. Soc. exp. Biol. (N.Y.), 72 (1949) 289.

HURST, E. W. and R. W. FAIRBROTHERS, Experimental vaccinial encephalitis in the monkey and the rabbit.
J. Path. Bact., 33 (1930) 463

HUTTER, A., Opmerkingen in de discussie aangaande de postvaccinale encephalomyelitis
Ned T. Geneesk., 74 (1930) 893

HUTTER, A., De constitutionele genese van postvaccinale encephalitis. *Ned T Geneesk.*, 96 (1952) 2381.

JACOB, H., Parainfektiose Encephalomyelitis und parainfektiose Encephalitis haemorrhagica (Strumpell-Leichtenstern) als zentralnervöse Komplikationen bei akuten Infektionskrankheiten
Nervenarzt, 19 (1948) 32

JACOB, H., Zur Frage der hyperergischen Encephalitis.
Ber Kongr. Neurol Tübingen, 1947, Stuttgart, 1949, pp 69–74

JACOB, H., Klinik und Pathologie der 'primaren' akuten haemorrhagischen Encephalitis.
Arch Psychiat Nervenkr., 184 (1950) 522.

JACOBS, H J., M G MAGIDA and D R. METCALF, Report of a case of postvaccinal encephalitis in a four-month-old child, with recovery.
J Pediat, 35 (1949) 94

JACOBSSON, E and B HOLMGREN, Encephalomyelitis complicating measles A clinical and electro-encephalographic study
Ann paediat (Basel), 173 (1949) 231.

JENNER, E., *An inquiry into the causes and effects of the variolae vaccinae.* London, 1798

JENSCH, K Untersuchungen uber die prämorbide Personlichkeit Encephalitis epidemica-Kranker und die genealogische Zusammensetzung ihrer engeren biologischen Familie
Z ges Neurol Psychiat, 168 (1940) 183

JERVIS, A and H KOPROWSKI, Experimental allergic encephalomyelitis
J Neuropath exp Neurol, 7 (1948) 319

JERVIS, A and H KOPROWSKI, Demyelinating encephalomyelitis in the dog, following antirabies vaccination
J Neuropath exp Neurol, 9 (1950) 113.

JULIUS, H W, Het vóorkomen van encephalitis postvaccinalis bij zeer jonge kinderen
Ned T Geneesk, 82 (1938) 4071

KABAT, E A, A WOLF and ADA E BEZER, Studies on acute disseminated encephalomyelitis produced experimentally in rhesus monkeys
J exp Med, 88 (1948) 417

KABAT, E A, A WOLF and ADA E BEZER, Studies on acute disseminated encephalomyelitis produced experimentally in rhesus monkeys, disseminated encephalomyelitis produced in monkeys with their own brain tissue
J exp Med, 89 (1949) 395

KALMIJN, D. *Abraham Capadose.*
Thesis, Univ. of Utrecht, 1955.
KAPSENBERG, JOHANNA G., *Het kweken van vaccinia-virus in geëxplanteerd weefsel.*
Thesis, Univ. of Amsterdam, 1955.
KESHMANSHINDER, S., Post-vaccinal encephalitis.
Proc. Alumni Ass. Edward VII Coll. Med., 3 (1950) 344.
KEYZER, J. L. en P. P. M. NIEUWENHUIS, Een 'epidemie' van meningo-myeloencephalitis postvaccinalis
Maandschr. Kindergeneesk., 15 (1947) 403
KEYZER, J. L., Een 'epidemie' van postvaccinale encephalitis in Tilburg
Ned. T. Geneesk., 93 (1949) 918
KEYZER, J. L., *Les accidents de la vaccination antivariolique.* Cours sur les vaccinations contre les maladies contagieux de l'enfance, organisé par le Centre Internationale de l'Enfance, Paris, 15 oct.-15 déc. 1951.
KING, JR. J. H. and R. L. FORREST, Vaccinia of the eyelids. Treatment by aureomycin in a second case
J. Amer. med. Assoc., 153 (1953) 31.
KLAY, D., *Inenting tegen pokken te Wageningen*
Ned. T. Geneesk., 96 (1952) 1545.
KNOPFELMACHER, W., Encephalitis postvaccinalis
Wien. klin. Wschr., 43 (1930) 97
KOKKEN, E., Encéphalite post-vaccinale mortelle. Démonstration anatomique
J. belge Neurol. Psychiat., 37 (1937) 696
KOKKEN, E., Encéphalite vaccinale et sérotherapie.
J. belge Neurol. Psychiat., 40 (1940) 454
KONYEY, E., Quelques problèmes concernant les méningites et encéphalomyélites à ultra-virus
Encéphale 38 (1949) 266
KOSTER, L., Acute diffuse glomerulonephritis na primovaccinatie tegen pokken
Ned. milit. geneesk. T. 6 (1953) 122.
KRAMER, P. H., Een geval van postvaccinale myelitis en de nieuwere afwijkingen bij postvaccinale encephalitis
Ned. T. Geneesk. 92 (1948) 3172.
KRAMER, P. H., Kliniek van de pokken (Report of a lecture in the Alg. Ned. Ver. v. soc. Geneesk., 19 nov. 1949)
T. soc. Geneesk. 28 (1950) 11
KRAMER, W., Een geval van encephalopathie na pokken
Ned. T. Geneesk., 93 (1949) 2981
KRETSCHMER, E., *Körperbau und Charakter. Untersuchungen zum Konstitutionsproblem und zur Lehre von den Temperamenten.* 21. u. 22. Aufl.
Springer, Berlin, 1955

LANGE, DE, see DE LANGE.

LAUBENTHAL, F., Über den Erbkreis der Ichthyosis vulgaris
Arch Derm Syph. (Berl), 179 (1939) 675.

LAUBENTHAL, F, Nervensystem und Ichthyosis (Erbbiologisch-pathogenetische Studien an Ichthyosissippen)
Z. ges. Neurol. Psychiat. 168 (1940) 722.

LAWLER, H J, Postvaccinal encephalitis in infancy.
J. Pediat. 37 (1950) 709

LEIFER, ADELHEID, Über postvaccinelle Encephalomyelitis.
Z ges Neurol. Psychiat. 164 (1939) 352

LEVADITI, C., Les ultravirus provocateurs des ectodermoses neurotropes.
Ann Inst Pasteur, 45 (1930) 673

LEVADITI, C., Rôle du 'neurovaccin' dans l'étiologie de l'encéphalite postvaccinale
Bull Acad roy Med Belg, 14 (1949) 399

LEVADITI, C., Au sujet de l'etiologie et du mécanisme pathogenique de l'encéphalite post-vaccinale.
Ann. Inst. Pasteur, 79 (1950) 711.

LEVADITI, C et S NICOLAU, Adaptation du virus vaccinal au névraxe.
C R Soc. Biol (Paris), 89 (1923) 363.

LEVADITI, C et S NICOLAU, Affinités de la neurovaccine
C R. Soc Biol. (Paris), 89 (1923) 484

LEVADITI, C et S NICOLAU, A propos de l'etiologie de l'encephalite postvaccinale
C R. Soc Biol (Paris), 94 (1926) 114.

LIGTERINK, J A. TH, Postvaccinale encephalitis, behandeld met adrenocorticotroop hormoon (ACTH).
Ned T Geneesk, 95 (1951) 3490

LITTLE, S. C and J. M AKIN, Meningoencephalitis due to virus of herpes simplex. Report of a case.
J. med Ass Alabama, 20 (1950) 115

LUMSDEN, C E., Experimental 'allergic' encephalomyelitis
Brain, 72 (1949) 198

LUMSDEN, C E, Experimental 'allergic' encephalomyelitis II. On the nature of the encephalitogenic agent
Brain, 72 (1950) 517

LUMSDEN, C E, E A KABAT, A WOLF and ADA E BEZER, Studies on acute disseminated encephalomyelitis produced experimentally in rhesus monkeys. Complement-fixing antibodies
J exp Med, 92 (1950) 253

LUXENBURGER, H, Der wesentliche Fortschritt auf dem Gebiete der psychiatrisch-neurologischen Erbforschung.
Fortschr Neurol Psychiat., 10 (1938) 44

MACARTHUR, P., Congenital vaccinia and vaccinia gravidarum
Lancet, 263 (1952) 1104.

MACINTOSCH, J. and R. W. SCARFF, The reaction of the central nervous system to vaccinia virus.
J. Path Bact, 33 (1930) 483.

MACRAE, J. and A. M G. CAMPBELL, Neurological complications of mumps.
Brit. Med. J., 2 (1949) 259.

MALL, J. H. W., W. CH M. VAN HINSBERGH en A HAMERS, Huidafwijkingen na vaccinatie
Ned. T. Geneesk., 99 (1955) 252

MARTIN, F., J. MACKEN et R. HESS, Sur une encéphalite subaiguë, ayant les caractères de la leuco-encéphalite sclérosante, avec inclusions. (Étude anatomoclinique, biologique et électro-encéphalographique de la première observation suisse)
Schweiz. Arch Neurol. Psychiat, 66 (1950) 217.

MEUNIER, M, Considérations cliniques sur l'encéphalite post-vaccinale infantile. Deux cas personnels
J. belge Neurol Psychiat, 37 (1937) 706.

MICHEJEW, W. W., Über akute demyelinisierende Encephalitis.
Nevropat. i Psihiat., 18 (1949) 25. (In Russian)
Abstract in. *Zbl. ges Neurol Psychiat.*, 3 (1950) 225

MORRISON, L. R, Disseminated encephalo-myelitis experimentally produced by the use of homologous antigen.
Arch Neurol. Psychiat. (Chicago), 58 (1947) 391.

MORRISON, L. R, Disseminated encephalo-myelitis experimentally produced by the use of homologous antigen
J nerv. ment. Dis, 107 (1948) 392

MORSIER, DE, see DE MORSIER.

MUMME, C, Zur Klinik und Pathologie der Nervenschädigungen nach Typhus-, Paratyphus- und Cholera-Schutzimpfungen.
Dtsch Z. Nervenheilk 164 (1950) 236

MUSAPH, H, Een geval van encephalitis na rode hond
Ned T. Geneesk., 91 (1947) 1141

NÉLIS, P, Contribution à l'étude de la vaccine et de l'encéphalite vaccinale Essais de prévention de cette complication.
Bull. Acad. roy Méd Belg 14 (1949) 210.

NETTER, A Encéphalite post-vaccinale ou vaccinale
Bull Acad Méd. Paris 102 (1929) 30

OLIN, G, Apparition de l'encéphalite post-vaccinal en Suède au cours des années 1924–1936
Bull Off int Hyg publ 30 (1938) 743

OLITSKY, P K and R H. YAGER, Experimental disseminated encephalomyelitis in white mice.
J. exp Med, 90 (1949) 213.
OLITSKY, P K. and R. H YAGER, Acute disseminated encephalomyelitis produced in albino mice
Proc. Soc exp Biol (N Y.), 70 (1949) 600.

PARREL, DE, see DE PARREL.
PASCHEN, E., Zur Frage der postvakzinalen Enzephalitis
Dtsch Med Wschr, 56 (1930) 219
PEERS, J H, Allergic encephalitis and its possible relationship to human disease
Amer. J clin Path, 20 (1950) 503.
PEETERS, H en M. G. NEURDENBURG, Statistiek der doodsoorzaken en postvaccinale encephalitis
Ned T. Geneesk, 82 (1938) 5851.
PETTE, H, Infektion und Nervensystem.
Dtsch Z. Nervenheilk., 110 (1930) 221.
PETTE, H., Das Problem der Entmarkungsenzephalomyelitiden in dynamischer Betrachtung
Klin Wschr, 24/25 (1947) 897.
PETTE, H, *Die akut entzündlichen Erkrankungen des Nervensystems (Viruskrankheiten, Entmarkungsenzephalomyelitiden, Neuritiden)*
Leipzig, 1942
PEUST, E, Konstitution, Veranlagung und Vererbung bei der Encephalitis Epidemica (Mit besonderer Berucksichtigung des Konstitutions- und Rassebegriffs)
J Psychol Neurol (Lpz), 37 (1929) 233
PIZON, P, L'encéphalite post-vaccinale
Rev Path comp, 49 (1949) 232
POLMAN, A, Anencephaly, spina bifida and hydrocephaly A contribution to our knowledge of the causal genesis of congenital malformation
Genetica, 25 (1949–50) 29
POLMAN, A, *De betekenis van het samenspel van gen en milieu voor de pathologie bij de mens*
Lecture in the Ned Anthropol Veren Rotterdam, 14-3-1953 (stencil)
POLMAN, A, *Erfelijke factoren bij Infectieziekten*
Lecture in the Ned Anthropol Veren Groningen, 14-5-1954 (stencil)
PUNTIGAM, F, Verursacht die Encephalitis post vaccinationem bei Jugendlichen kriminogene Personlichkeitsveranderungen?
Öst. Z. Kinderheilk, 4 (1950) 142
PUNTIGAM, F und K BERGER, Bietet die mit Erfolg durchgeführte Pockenschutzimpfung einen Schutz vor Lähmungen bei Poliomyelitis?
Wien med Wschr, 106 (1956) 412

PUNTIGAM, F. and J. DAIMER, Beobachtungen bei Pockenschutz-Wiederimpfungen von Personen, die eine Erkrankung an Encephalitis postvaccinationem durchgemacht haben.
Öst. Z. Kinderheilk., 4 (1950) 6.

RADERMECKER, J. et J. MACKEN, Remarques sur quelques déterminations inflammatoires non-suppurées du système nerveux
Acta neurol. belg., 53 (1953) 152.

REHSTEINER, R. und E. WIESMANN, Vaccine-Antikorper-Nachweis im Serum nach reaktionsloser Vaccination und Impf-Encephalitis
Ann. paediat. Basel, 172 (1949) 230

REISCH, O., Zur Klarung der Bedingungen für das Auftreten der Encephalitis post vaccinationem.
Wien. klin. Wschr., 43 (1930) 103.

Report of a Committee appointed to investigate the possible harmful consequences of vaccination, among Dutch physicians (In Dutch)
Ned. T. Geneesk., 36 (1902) 1361.

Report (general and cumulative) of the Encephalitis Committee. (In Dutch)
Ed. by the President of the Board of Health (N. M. JOSEPHUS JITTA), 's-Gravenhage, 1932.

RIGOTTI, A., Sulla encefalomielite postvaccinia nell'adulto, con particolare riguardo alla sua posizione nosografica tra le malattie demielinizzanti.
Riv. Neurol., 19 (1949) 1.

RIMBAUD, L., P. PASSOUANT et G. VALLAT, Les encéphalites comateuses.
Presse méd., 59 (1951) 605

RIVERS, T. M. and F. F. SCHWENTKER, Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys.
J. exp. Med., 61 (1935) 689

ROSEN, A. P. and R. A. JAWORSKI, Postvaccination encephalitis. A problem in differential diagnosis.
Amer. J. Dis. Child., 78 (1949) 248

RUPPERDA WIERDSMA, A., *Encephalitis postvaccinationem, allergie en huid*
Thesis, Univ. of Leyden, 1932

SCHACHTER, M., Encéphalopathies et troubles caractériels à la suite des brûlures chez l'enfant
Acta psychiat. scand., 25 (1950) 285

SCHNEIDER, H., Zur Klinik und Pathogenese des 'Meningismus'-Syndroms und der parainfektiösen Encephalitis
Wien. Arch. inn. Med. 35 (1941) 1

SCHREUDER, J. TH. R., TH. G. VAN RIJSSEL and J. D. VERLINDE, Encephalomyelitis na besmetting met koepokken
Ned. T. Geneesk. 94 (1950) 2603

SCHULTZ, M., *Impfung, Impfgeschäft und Impftechnik* Berlin, 1891.
SCHWARTZ, M., *Heredity in bronchial asthma A clinical and genetic study of 191 probands and 50 probands with Baker's asthma* Copenhagen, 1952
SCHWEIGHOFER, J., Die nervose Anlage I.
Z. ges Neurol Psychiat, 109 (1927) 585.

of the literature.
Indiana med. Ass, 42/12 (1949), 1254–1257 (3 tables)

Si

nervosen Impfschäden.
Dtsch. med. Wschr., 82 (1957) 2061.
SILLEVIS SMITT, W G, *Over den vormenrykdom van heredodegeneratieve verschijnselen Makro- en mikroheredodegeneraties van het C Z.S*,
Thesis, Univ. of Utrecht, 1935.
SILLEVIS SMITT, W G, Degeneration and stigmata degenerationis,
Folia psychiat. neerl, 54 (1951) 175
SILLEVIS SMITT, W G, De praeventie van postvaccinale encephalitis
Ned T. Geneesk, 96 (1952) 554.
SMEETS, M. A J G. H and J M SOETERS, Verwikkelingen na inenting tegen pokken
Maandschr Kindergeneesk, 19 (1951/52) 325
SPIELMEYER, W, *Ein Beitrag zur Kenntnis der Encephalitis*, Berlin, 1902
SPIELMEYER, W, *Histopathologie des Nervensystems* Berlin, 1922
STENCZEL, J, Pockenschutzimpfung
Ars medici (Gand), 43 (1953) 760
STEVENSON, L D, The pathology of encephalitis.
In J B NEAL *et al.*, *Encephalitis, a Clinical Study* Grune & Stratton, New York, 1942, pp 385–521
STOPPELMAN, M R H, Stoornissen tijdens de zwangerschap en aangeboren afwijkingen.
Ned T. Geneesk, 98 (1954) 3641.
STRÖMGREN, E, *Beiträge zur psychiatrischen Erblehre auf Grund von Untersuchungen an einer Inselbevölkerung* Copenhagen, 1938.
STRÖMGREN, E., Erbpsychiatrische Forschungen der letzten Jahre in den nordischen Ländern.
Schweiz Arch Neurol Psychiat, 62 (1948) 378.
STUART, J., Memorandum on postvaccinal encephalitis.
Bull Org mond Santé, 1 (1947–'48) 36

THOMAS, E., Vakzination, Spätreaktion und Spätenzephalitis.
Dtsch. med. Wschr, 60 (1934) 1673.

THOMAS, L., PHI Y. PATERSON and BETTY SMITHWICK, Acute disseminated encephalomyelitis following immunization with homologous brain extracts. I Studies on the rôle of a circulating antibody in the production of the condition in dogs
J. exp. Med., 92 (1950) 133.

TROSTDORF, E. Über Encephalomyelitis postvaricellosa als Beitrag zur Frage der Neuroallergie.
Dtsch. Z. Nervenheilk., 159 (1948) 332.

TURNBULL, M. and J. MACINTOSH, Encephalo-myelitis following vaccination.
Brit. J. exp. Path, 7 (1926) 171.

UIBERALL, E., Complicaciones neurológicas de la vacunatión antivariólica en Santiago de Chile.
Rev. méd. Chile, 78 (1950) 588

VAN BOGAERT, L., Les manifestations nerveuses au cours des maladies éruptives (varicelle, rougeole, scarlatine)
Rev. neurol, 1 (1933) 150.

VAN BOGAERT, L., Introduction au problème de l'encéphalite vaccinale.
J belge Neurol Psychiat., 37 (1937) 675.

VAN BOGAERT, L., Sur la valeur et la signification de quelques corrélations d'hérédodégenérescences.
Encéphale, 37 (1948) 1

VAN BOGAERT, L., Las encefalitis de la sustancia blanca.
Actas luso-esp Neurol, 8 (1949) 87.

VAN BOGAERT, L., Problemas téoricos planteados por las encefalitis de los exantemas y de la vacunacion antivarioloca.
An Med Cir (Barcelona), 26 (1949) 289

VAN BOGAERT, L., Über funktionelle Kreislaufstörungen des Zentralnervensystems und das Problem der postvaccinalen Encephalitis.
Arch Psychiat Nervenkr, 185 (1950) 482

VAN BOGAERT, L., Post-infectious encephalomyelitis and multiple sclerosis The significance of perivenous encephalopathy.
J Neuropath exp Neurol 9 (1950) 219.

VAN BOUWDIJK BASTIAANSE, F S., *Die in Holland beobachteten Fälle von Encephalomyelitis postvaccinalis bis zum 1. Januar 1929*
Z ges Neurol Psychiat, 134 (1931) 657

VAN BOUWDIJK BASTIAANSE, F S., L'encephalomyélite postvaccinale
Revue neur 1 (1932) 825

VAN BOUWDIJK BASTIAANSE, F. S., L'encéphalite postvaccinale aux Pays-Bas
J. belge Neurol. Psychiat., 37 (1937) 685
VAN BOUWDIJK BASTIAANSE, F. S., Neuralgieën na re-vaccinatie
Ned. T. Geneesk., 95 (1951) 3065
VAN BOUWDIJK BASTIAANSE, F. S., On the difference between the encephalomyelitis following revaccination during partial immunity, and the well-known picture after primary vaccination (Clinico-pathological observations)
Folia psychiat. neerl., 58 (1955) 147.
VAN DER DOES DE WILLEBOIS, J. J. M., *Over migraine, in het bijzonder over hemicrania psychica*
Thesis, Univ. of Utrecht, 1932
VAN GEHUCHTEN, P. et M. FALCON, Etude anatomo-clinique d'un cas d'encéphalite postvaccinale
J. belge Neurol. Psychiat., 38 (1938) 932
VAN DER HORST, L., *Anthropologische psychiatrie*, 2 Volumes, Amsterdam, 1946
VAN DER HORST, L., Considérations comparatives sur les encéphalitides par rapport à la vaccination contre la coqueluche
Folia psychiat. neerl., 53 (1950) 710
VAN WAYENBURG, G. A. M., Revaccineringsneuralgieën
Ned. T. Geneesk., 60 (1916) 1528.
VAN DER WIEL, H. J., *Inheritance of glioma*
Elsevier, Amsterdam, 1960
VAN WULFFTEN PALTHE, P. M. and G. J. PUISTER, Primovaccinatie en electro-encephalographisch patroon
Ned. T. Geneesk., 101 (1957) 1344
VERHAART, W. J. L., Encephalitis of Batavia.
Acta psychiat. scand., 24 (1949) 135
VERLINDE, J. D., *Encephalitis bij den hond. Een vergelijkend-pathologisch onderzoek naar de aetiologie van de z.g. post-infectieuze encephalitides*
Thesis, Univ. of Utrecht, 1939
VERLINDE, J. D., Encephalitis postvaccinalis. Geeft de combinatie van de vaccinia-virus- en van de activeringstheorie een verklaring voor haar ontstaan?
Ned. T. Geneesk., 99 (1955) 1020
VILLINGER, W., Konstitutionelle Disposition zur Encephalitis epidemica
Münch. med. Wschr., 68 (1921) 913
VRIES, DE, see DE VRIES

WAGNER-JAUREGG, J., Über erbliche Belastung
Wien. klin. Wschr., 44 (1902) 1155
WAYENBURG, VAN, see VAN WAYENBURG